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# CONTENTS OF VOL. 209

## ORIGINAL ARTICLES

### No. 1—JANUARY

Diabetes Mellitus as Observed in 100 Cases for 10 or More Years. I. General Observations. By RUSSELL RICHARDSON, M.D., and MORRIS A. BOWIE . . . . .	1
Diabetes Mellitus as Observed in 100 Cases for 10 or More Years. II. Cardiac Studies. By JOSEPH EDEIKEN . . . . .	8
Diabetes Mellitus as Observed in 100 Cases for 10 or More Years. III. Ocular Findings. By IRVING H. LEOPOLD . . . . .	16
Diabetes Mellitus as Observed in 100 Cases for 10 or more Years. IV. Peripheral Vascular Findings in 89 of These Cases. By MEYER NAIDE, M.D. . . . .	23
Gelatin as a Plasma Substitute. The Effect of Gelatin Infusion on the Subsequent Typing and Cross-matching of the Blood, With a Method of Eliminating the Phenomenon of Pseudoagglutination. By C. EVERETT KOOP, M.D., and LOUISA BULLITT . . . . .	28
Digilanid and the Therapy of Congestive Heart Disease. By A. B. RIMMERMAN, M.D. . . . .	33
An Epidemic of Pleurodynia With Prominent Neurologic Symptoms and No Demonstrable Cause. By JEANNETTE McCONNELL, M.D. . . . .	41
The Relationship of Cold Agglutinins to the Course of Primary Atypical Pneumonia. By CAPT. CRICHTON McNEIL, M.C., A.U.S. . . . .	48
SYMPOSIUM ON AIR-BORNE INFECTIONS (See also 6 articles in February issue):	
1. Atypical Pneumonia. By the COMMISSION ON ACUTE RESPIRATORY DISEASES . . . . .	55
2. Factors in the Control of the Spread of Acute Respiratory Infections With Reference to Streptococcal Illness and Acute Rheumatic Fever. By LIEUT. STAFFORD M. WHEELER, (MC) USNR, and T. DUCKETT JONES, M.D. . . . .	58
3. Scarlet Fever as an Air-borne Infection. By LIEUT. HORACE L. HODES, (MC) USNR, LIEUT.-COMDR. FRANCIS F. SCHWENTKER, (MC) USNR, LIEUT. BEACH M. CHENOWETH, JR., (MC) USNR, and LIEUT. JOHN L. PECK, JR., (MC) USNR . . . . .	64
4. The Transmission and Control of Meningococcal Infections. By JOHN J. PHAIR, and MAJOR EMANUEL B. SCHOENBACH, M.C., A.U.S. . . . .	69
5. The Control of Meningococcal Meningitis by Mass Chemoprophylaxis With Sulfadiazine. By LIEUT.-COMDR. F. S. CHEEVER, (MC) USNR . . . . .	74
6. Mumps and Chickenpox as Air-borne Diseases. By KARL HABEL . . . . .	75
Inadequate Action of Penatin Against <i>Brucella Abortus in Viro</i> . By E. L. STUBBS, I. LIVE, F. G. SPERLING, and W. KOCHOLATY . . . . .	78

## No. 2—FEBRUARY

Filariasis in Soldiers on an Island in the South Pacific. By CAPT. THEODORE D. ENGLEHORN, M.C., A.U.S., and LIEUT. WILLIAM E. WELLMAN, M.C., A.U.S. . . . .	141
SYMPOSIUM ON AIR-BORNE INFECTIONS (Continued):	
7. Summary of a 3-Year Study of the Clinical Applications of the Disinfection of Air by Glycol Vapors. By T. N. HARRIS, M.D., and JOSEPH STOKES, JR., M.D. . . . .	152
8. Experimental Air-borne Tuberculosis. By MAX B. LURIE, M.D. . . . .	156
9. The Present Status of Glycol Vapors in Air Sterilization. By MORTON HAMBURGER, JR., M.D., O. H. ROBERTSON, M.D., and THEODORE T. PUCK, PH.D. . . . .	162
10. Recent Studies on the Control of Dust-borne Bacteria by Treatment of Floors and Bedclothes With Oil. By MAJOR CLAYTON G. LOOSLI, M.C., A.U.S., and O. H. ROBERTSON, M.D. . . . .	166
11. Sampling Devices. By H. G. DU BUY, and ALEXANDER HOLLAENDER . . . . .	172
12. Measurement of Air-borne Infection by the Disinfection of Air. By W. F. WELLS . . . . .	177
The Incidence of Sicklemia and Sickle Cell Anemia in 3000 Canal Zone Examinations Upon Natives of Central America. By MAJOR WRAY J. TOMLINSON, M.C., A.U.S. . . . .	181
Studies of Plasma Volume in the Human Being. Comparative Results of Reduction of Plasma Volume, Intramuscular Pressure and Venous Pressure in Surgical Shock. By CAPT. HENRY H. HENSTELL, M.C., A.U.S., and COMDR. LEWIS GUNTHER, (MC) USNR . . . . .	187
Aberrant Atrio-ventricular Conduction in a Case Showing a Short P-R Interval and an Abnormal But Not Prolonged QRS Complex. By THEODORE T. FOX, M.D. . . . .	199
The Significance of the Pulmonary Diastolic Murmur in Cases of Mitral Stenosis. By ALDO A. LUISADA, M.D., and LOUIS WOLFF, M.D. . . . .	204
Spontaneous Mediastinal Emphysema With Pneumothorax Simulating Organic Heart Disease. By CAPT. HENRY MILLER, M.C., A.U.S. . . . .	211
A Method for Measuring Small Amounts of Weight Loss in Man. By G. E. BURCH, M.D. . . . .	220
The Relation of Total Insensible Loss of Weight to Water Loss From the Skin and Lungs of Human Subjects in a Subtropical Climate. By G. E. BURCH, M.D., and TRAVIS WINSOR, M.D. . . . .	226
Use of Posterior Pituitary Extract in Tests of Urinary Concentration. By R. D. TAYLOR, M.D., JAMES D. PEIRCE, M.D., and IRVINE H. PAGE, M.D. . . . .	235
Somatic Pain. Diagnostic and Therapeutic Aspects of Local Infiltration. By BERNARD JUDOVICH, M.D. . . . .	240

## No. 3—MARCH

Some Clinical Observations on an Outbreak of Jaundice Following Yellow Fever Vaccination. By LT.-COL. JOSEPH M. HAYMAN, JR., M.C., and MAJOR WILLIAM A. READ, M.C. . . . .	281
--	-----

Anaërobic Septicemia. Report of 6 Cases With Clinical Bacteriologic and Pathologic Studies. By J. DOUGLAS REID, Sc.D., GEORGE E. SNIDER, M.D., ELAM C. TOONE, M.D., and JOHN S. HOWE, M.D. . . . .	296
The Coincidence of Allergic Disease, Unexplained Fatigue, and Lymphadenopathy; Possible Diagnostic Confusion With Infectious Mononucleosis. By THERON G. RANDOLPH, M.D., and ROBERT A. HETTIG, M.D. . . . .	306
The Use of Bromsalizol in Lengthening the Effect of a Sympathetic Nerve Block. By FERDINAND C. LEE, M.D., DAVID I. MACHT, M.D., and ROSS Z. PIERPONT, M.D. . . . .	314
Spermatogenic Activity of Various Steroids. By G. MASSON, Ph.D. . . . .	324
Meigs' Syndrome in a Case of Multilocular Pseudomucinous Cystadenoma of the Ovary. By JOSEPH MILLETT, M.D., and JOHN SHELL, M.D., F.A.C.S. . . . .	327
A Relation Between Cell-pack (Hematocrit) Volumes and Lymphocyte Counts. By FREDERIC T. JUNG, Ph.D., M.D., OPAL E. HEPLER, Ph.D., M.D., and MASON S. MAYNARD, M.D. . . . .	336
Pernicious Anemia and Carcinoma of the Stomach—Autopsy Studies Concerning Their Interrelationship. By HENRY S. KAPLAN, M.D., and LEO G. RIGLER, M.D. . . . .	339
Coronary Insufficiency, Revealed by Ectopic Nodal and Ventricular Beats in the Presence of Left Bundle Branch Block. By ERNST SIMONSON, M.D., NORBERT ENZER, M.D., F.A.C.P., and JAY S. GOODMAN, M.D. . . . .	349
Large Interauricular Septal Defect With Particular Reference to Diagnosis and Longevity. Report of 2 New Cases. By JOHN B. BURRETT, M.D., and PAUL D. WHITE, M.D. . . . .	355
Developments in Arthritis. By RALPH PEMBERTON, M.D. . . . .	364
Poliomyelitis in Pregnancy. By MAX J. FOX, M.D., and LOUIS SENNETT, M.D. . . . .	382

## No. 4—APRIL

Complications Arising in Donors in a Mass Blood Procurement Project. By MARY HEISS BOYNTON, M.D., and MAJOR EARL S. TAYLOR, M.C., A.U.S. . . . .	421
The Use of a "Modified Globin" From Human Erythrocytes as a Plasma Substitute. Preliminary Report. By MAX M. STRUMIA, M.D., F. W. CHORNOCK, Ph.D., ALTON D. BLAKE, M.D., and WALTER G. KARR, Ph.D. . . . .	436
Hemophilia-like Disease in the Female. With a Note on the Clotting Time of the Recalcified Plasma. By FREDERICK W. MADISON, M.D., and ARMAND J. QUICK, Ph.D., M.D. . . . .	443
Cardiac Hypertrophy and Extramedullary Erythropoiesis in Newborn Infants of Prediabetic Mothers. By HERBERT C. MILLER, M.D. . . . .	447
Acute Myocarditis in Influenza A Infections. Two Cases of Non-bacterial Myocarditis, With Isolation of Virus From the Lungs. By MAXWELL FINLAND, M.D., FREDERIC PARKER, JR., M.D., MILDRED W. BARNES, A.M., and CAPT. LESLIE S. JOLIFFE, M.C., A.U.S. . . . .	455
Provocative Prolongation of the P-R Interval in Rheumatic Fever. By RICHARD GUBNER, M.D., MURRILL SZUCS, M.D., and HARRY E. UNGERLEIDER, M.D., F.A.C.P. . . . .	469

The Primary Influence of Basal Vascular Tone on the Development of Post-occlusive Collateral Circulation and in Selecting Patients for Sympathectomy. By MEYER NAIDE, M.D., and ANN SAYEN . . . . .	478
A Fatal Case of Cerebral Coccidioidomycosis With Cultural Studies. By CAPT. HANS G. SCHLUMBERGER, M.C., A.U.S. . . . .	483
Pneumococcic Pneumonia Resembling Primary Atypical Pneumonia. By E. RACKER, M.D., S. P. ROSE, M.D., and A. O. TUMEN, M.D. . . . .	496
Roentgen Therapy of Boeck's Sarcoid. By ERNST A. POHLE, M.D., PH.D., LESTER W. PAUL, M.D., and ELIZABETH A. CLARK, M.D. . . . .	503
The Treatment of Tularemia With Intravenous Bismuth Sodium Tartrate. By WILL W. JACKSON, M.D. . . . .	513
Vitamin Content of Liver Extracts for Parenteral Use. A Comparison of Crude and Concentrated Preparations. By GUY W. CLARK, PH.D. . . . .	520

### No. 5—MAY

A Severe Type of Hereditary Anemia With Elliptocytosis, Interesting Sequence of Splenectomy. By THOMAS B. COOLEY, M.D., Sc.D. . . . .	561
The Frequency of Thalassemia. By JAMES V. NEEL, PH.D., M.D., and WILLIAM N. VALENTINE, M.D. . . . .	568
Eosinophilia Following Parenteral Liver Therapy. Literature and Case Report. By HAROLD A. HANNO, M.D., and MAURICE MENSCH, M.D. . . . .	572
The Prognostic Value of Marrow Eosinophils in Thrombocytopenic Purpura. By STEVEN O. SCHWARTZ, M.D. . . . .	579
Infectious Mononucleosis and the Negro. With a Report of 6 Cases. By ALEXANDER BLAIN, 3RD, M.D., and ELMORE C. VONDER HEIDE, M.D. . . . .	587
Spontaneous Pneumothorax as a Complication of Pneumonia in Adults. By CAPT. ELI R. MOVITT, M.C., A.U.S. . . . .	595
The Hepatotoxic Action of Diethylstilbestrol With Report of a Case. By HERBERT ELIAS, M.D., and DAVID SCHWIMMER, M.D. . . . .	602
The Enhancement of the Plasma Concentration of Penicillin in Dogs by the Simultaneous Administration of Para-aminohippuric Acid, III. By KARL H. BEYER, PH.D., M.D., W. F. VERWEY, Sc.D., ROLAND WOODWARD, B.S., LAWRENCE PETERS, PH.D., and PAUL A. MATTIS, D.Sc. . . . .	608
The Antistaphylococcal Activity of Various Sulfonamides. With a Method for Routine Determination of Chemotherapeutic Activity. By N. ERCOLI, M. N. LEWIS and ELEANOR M. HARKER . . . . .	621
Persistence of Pneumococci in Sulfonamide Treated Cases of Pneumonia. By CAPT. ROBERT A. GOODWIN, JR., M.C., A.U.S., CLAIR WILCOX and MAXWELL FINLAND, M.D. . . . .	628
A Clinical Study of Sensitivity to Sulfathiazole. By GERALD T. KENT, M.D., and HERBERT W. DIEFENDORF, M.D. . . . .	640
Failure of Penicillin in Rheumatoid Arthritis. By BERNARD I. COMROE, M.D. . . . .	646
Focal Electroencephalographic Changes During the Scotomas of Migraine. By GEORGE L. ENGEL, M.D., EUGENE B. FERRIS, JR., M.D., and JOHN ROMANO, M.D. . . . .	650

Initial Cardiac Examination of 23,000 Inductees and Volunteers. By NATHAN FLAXMAN, M.D. . . . .	657
Acute Syphilitic Meningitis. A Discussion of the Problems Encountered in the Diagnosis. By ALBERT HEYMAN, M.D. . . . .	664
Joint Disease Associated With Acromegaly. By HANS WAINE, M.D., GRANVILLE A. BENNETT, M.D., and WALTER BAUER, M.D. . . . .	671

## No. 6—JUNE

The Therapeutic Use of Radioactive Phosphorus. By COMDR. SHIELDS WARREN, (MC) USNR . . . . .	701
Radioactive Phosphorus in the Treatment of Polycythemia Vera. Results and Hematologic Complications. By BYRON E. HALL, M.D., CHARLES H. WATKINS, M.D., MALCOLM M. HARGRAVES, M.D., and HERBERT Z. GIFFIN, M.D. . . . .	712
Recent Studies on Yellow Bone Marrow Extracts. By J. E. CALDWELL, R. H. SIFFERD, Ph.D., J. D. PORSCHKE, Ph.D., and F. FENGER, Ph.D. . . . .	717
Abdominal Crises in Uncomplicated Sickle Cell Anemia. A Clinico-pathologic Study of 11 Cases With a Suggested Explanation of Their Cause. By MAJOR WRAY J. TOMLINSON, M.C., A.U.S. . . . .	722
The Artificial Production and Significance of Target Cells. With Special Reference to Their Occurrence in Thalassemia (Cooley's Erythroblastic Anemia). By WILLIAM N. VALENTINE, M.D., and J. V. NEEL, M.D., Ph.D. . . . .	741
A Case of Eczema as a Source of a Streptococcal Epidemic. By G. K. DEFORREST, M.D., and LORAIN M. KERR . . . . .	752
The Effect of Simultaneous Tuberculous Infection on Experimental Trichinella Infestations in Guinea Pigs. By O. T. DAVIS, M.D., GEORGE T. HARRELL, M.D., and E. S. KING, M.D. . . . .	758
Clinical Aspects of Pain in the Chest. II. Pain Arising From the Esophagus. By TINSLEY R. HARRISON . . . . .	765
Clinical Aspects of Pain in the Chest. III. Pain Arising From the Stomach. By TINSLEY R. HARRISON . . . . .	771
Penicillin in the Treatment of Intractable Bronchial Asthma. A Preliminary Report. By SIMON S. LEOPOLD, M.D., and ROBERT A. COOKE, M.D. . . . .	784

## NEW BOOKS AND NEW EDITIONS

Book Reviews and Notices . . . . .	131, 273, 415, 551, 696, 817
New Books . . . . .	138, 278, 419, 559, 698, 821
New Editions . . . . .	139, 279, 420, 560, 699, 822

## PROGRESS OF MEDICAL SCIENCE

MEDICINE . . . . .	86
Leptospirosis. By EMILE A. BERTUCCI, JR., M.D. . . . .	

NEUROLOGY AND PSYCHIATRY . . . . .	111
Relationship and Function of the Pyramidal Tract. By ALBERT J. LUBIN, M.D.	
SURGERY . . . . .	253
Refrigeration in Surgery. By C. G. JOHNSTON, M.D.	
OPHTHALMOLOGY . . . . .	257
Retinopathy in Glomerulonephritis. By H. P. WAGENER, M.D.	
PATHOLOGY AND BACTERIOLOGY . . . . .	388
The Relation of Streptococci to Human Disease: Importance of Identification and Nomenclature. II. Streptococci Other Than Those of Group A. By J. HOWARD BROWN, Ph.D., and ISABELLE G. SCHAUB	
PREVENTIVE MEDICINE AND EPIDEMIOLOGY . . . . .	395
Seasonal Prevalence as a Principle in Epidemiology. By W. LLOYD AYCOCK, M.D., GRACE E. LUTMAN, M.D., and GEORGE E. FOLEY	
DERMATOLOGY AND SYPHILOLOGY . . . . .	525
Biologic False Positive Reactions to the Tests for Syphilis. By HERMAN BEERMAN, M.D.	
OTO-RHINO-LARYNGOLOGY . . . . .	542
The Tonsil-Adenoid Problem. By NOAH D. FABRICANT, M.D.	
RADIOLOGY . . . . .	688
Notes on a Variety of Roentgenologic Problems. By HARRY M. WEBER, M.D.	
PEDIATRICS . . . . .	788
The Intra-duodenal Secretions in Childhood. By IRVING J. WOLMAN	
GYNECOLOGY AND OBSTETRICS . . . . .	804
The Rh Factor in Pregnancy. By CATHARINE B. HESS, M.D.	
PHYSIOLOGY:	
Proceedings of the Physiological Society of Philadelphia	127, 267, 411, 548, 692, 813

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1945

## ORIGINAL ARTICLES

### DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

#### I. GENERAL OBSERVATIONS

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THIS paper, and those immediately following, present a study in this clinic of 100 patients, with diabetes for 10 years or more. This investigation was undertaken because these patients have been under close supervision in the clinic for many years and because, during these years, they have been maintained on a diet in which the carbohydrate has been increased and the fat decreased, compared with diets previously in general use. We do not know of other investigations based on material of this nature, all studied for more than 10 years.

It seemed also that examinations of the heart, eyes and peripheral circulation in these patients, over a period of years, might add to our knowledge of the influence of long-standing diabetes on these organs.

Certain observations are given regarding the diet and insulin prescribed and the complications encountered in these patients.

*Methods.* The patients in this series comprise the first 100 persons, with diabetes of more than 10 years duration, who made clinic visits after the investigation was started. Some of them had attended the clinic for many years, while others had only recently completed 10 years of treatment when reviewed by us.

They were first examined in the Metabolic Clinic and were then referred to the Cardiac, the Peripheral Vascular and the Ophthalmologic Clinics. Examinations in these clinics were made with especial reference to the diabetes.

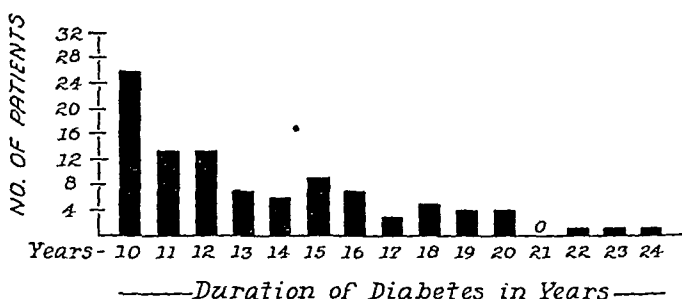
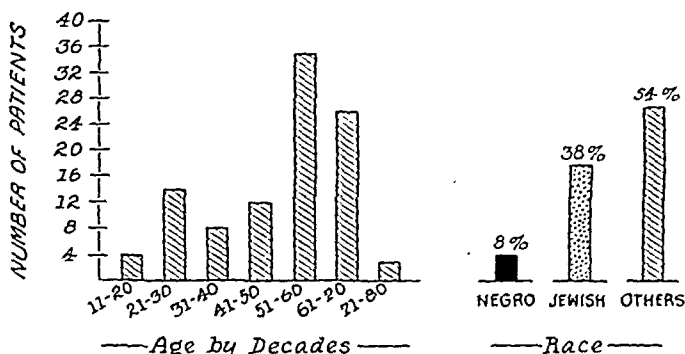
During the past 15 years or more these patients had been taking a diet in which the fat varied between 70 and 110 gm., with an average of about 90 gm., and the carbohydrate had been between 125 and



200 gm. The protein formerly had been given as 1 gm. per kilo of body weight. This has been gradually increased during recent years to an average of a little over 70 gm. daily.

The blood sugar determinations were done by the method of Folin and Malmros<sup>1</sup> adapted to the Evelyn photoelectric colorimeter, and the cholesterol determinations by a modification of Bloor's method.<sup>2</sup>

### Age and Race of Patients and Duration of Diabetes.



GRAPH 1

*Age Distribution by Decades and Duration of Diabetes.* In Graph 1 is shown the age distribution of these patients at the time of study according to decades. As is usually the case in diabetes, the greater number is found in the later decades of life. Men comprised 25% and women 75% of the group. The distribution of these patients according to race and the duration of diabetes is also shown in Graph 1. Although the 26 patients with diabetes for exactly 10 years make up the largest single group, 74% of the total number had diabetes for a still longer time.

TABLE 1.—BODY WEIGHT OF PATIENTS IN THIS SERIES

Weight	No. patients
More than 10% below normal . . . . .	15
10% below to 10% above normal . . . . .	67
11% above to 20% above normal . . . . .	9
More than 20% above normal . . . . .	9

*Body Weight of Patients.* In this clinic every attempt has been made to keep the patients' weight a few pounds below the normal for height, sex and age. In Table 1 is shown the weight of the patients in this series at the end of the 10 year period.

Of these patients, 82 maintained a satisfactory weight for diabetic patients, and 18 were above normal. This far from ideal figure is in part explained by the ignorance of the markedly overweight patients, though it still remains a blot on the educational record.

*Heredity.* On careful questioning, it appears that only 49% of this group knew of any relatives with diabetes. The familial incidence is probably too low, as relatives of many of the patients were still in Europe and accurate information was not obtainable, and because the history of familial diabetes is less adequate in adults than in children, who were few in this series.

*Hospitalization.* It has been the rule of this clinic to hospitalize all patients having severe complications or other acute conditions. Other patients were taken into the wards for adjustment of the diet and insulin and for instruction, as accommodations allowed. Of the group, 61% have at some time been taken into the wards, while 39% have been controlled by visits to the clinic without any stay in the hospital.

*Acidosis.* Acidosis with coma has been present in the histories of 26 of the patients. Most of these occurred before the patient came under the care of the clinic. Of the 26 patients, 17 had acidosis more than 10 years ago, 6 had acidosis at the time when diabetes was diagnosed, and 3 during the past 10 years. All of these recovered. The patients are taught that acidosis is probably the most dangerous of the complications of diabetes.

In addition to the 3 patients who had acidosis and coma during the past 10 years, 3 others had this condition while attending the clinic before that period. All but one of these occurred before the patients were 20 years old. Three of them had acidosis before their 10th year of age, 1 at 18 and 1 at 19 years of age. One woman developed acidosis at 55 with a carbuncle on her neck. All of these patients are now living and doing well.

*Severity and Control of Diabetes.* In order to investigate any possible influence exerted by the severity of the diabetes or by the effectiveness of its control, these patients have been arranged under both categories. As there is no satisfactory criterion of the severity of the diabetes, we have used the daily insulin requirement for this purpose. By this means we have divided the patients into 4 groups. In the 1st group are included those who took no insulin; in the 2nd group those using up to 25 units daily; in the 3rd group are those taking from 25 to 50 units; while the 4th group consists of those patients who required 50 or more units daily.

In a similar manner, they have also been divided into 4 groups on the basis of the control of diabetes. This has been determined by the averages of all blood sugar determinations made during the years 1934 and 1939, these 2 years being arbitrarily selected. In each patient,

16 or more blood sugar determinations were used to obtain each of these averages.

The 1st group includes those patients whose average blood sugar for the years stated was below 140 mg. per 100 cc.; in the 2nd those with average blood sugars between 140 and 180; the 3rd group, those from 180 to 250; and the 4th group those with average blood sugar determinations of 250 mg. per 100 cc. or more. In Table 2 are shown the number of patients in each of these groups.

TABLE 2.—CORRELATION BETWEEN THE DEGREE OF DIABETES AND ITS CONTROL

Degree of diabetes in terms of insulin requirement (units per day)	% of cases	% of cases	State of control of diabetes in terms of range of blood sugar (mg. per 100 cc. blood)
None	19	20	<140
5-24	31	40	140-180
25-49	22	32	181-250
50 or more	28	8	>250

It will be noted that all degrees of diabetes are well represented. As regards the diabetic control, it will be seen that 60% of the patients have maintained averages of blood sugar under 180 mg., which is generally considered to represent a fairly satisfactory state of adjustment. Only 8% of them are in what might be considered a poor state of adjustment. It appears from the figures in this table that the most severe diabetics have developed greater skill and care in their control.

Review of the records of these 8 patients fails to show any higher incidence of complications than has been present in patients who maintained a satisfactory diabetic adjustment. The group, however, is too small to allow any definite conclusions to be drawn.

Using the above classifications, the severity of the diabetes and the state of adjustment have been related to the duration of the diabetes. The factor of duration of diabetes apparently has no relation to its severity or to the success with which the patient maintains control.

*Change in Patients After 5 Year Period.* In order to determine what changes might have occurred in the patients and in our treatment of them over a period of years, certain data were collected. The data shown in Table 3 were taken from the records of 2 separate years, which were 5 years apart. The years selected were 1934 and 1939. The figures given are averages of all observations made during these 2 years. All patients had had diabetes for at least 5 years before the first observations shown in the table.

TABLE 3.—CHANGE IN 100 PATIENTS AFTER A SELECTED 5 YEAR PERIOD

	Year	
	1934	1939
Average diet:		
Protein . . . . .	68	73
Fat . . . . .	81	82
Carbohydrate . . . . .	142	162
Number taking insulin . . . . .	55	79
Average insulin dose per patient (units) . . . . .	51	55
Average blood sugar (mg. per 100 cc.) . . . . .	192	157
Average serum cholesterol (mg. per 100 cc.) . . . . .	286	237

The average blood sugar and serum cholesterol figures show that there was a slight but definite improvement in the control of all patients in the group. These averages appeared to result from the improvement of the diabetes in some of the patients, and from the better adjustment with increased use of insulin in others. Although both of these factors were evident, it was not possible to separate them for statistical study.

Of the 55 patients taking insulin at the beginning of the 5 year period, 10 took less insulin, 24 took the same amount, and 21 required more insulin at the end than at the beginning of the 5 years. Of the 45 patients who took no insulin at the beginning, 21 still did not require it at the end of the period, while 24 began the use of insulin during the 5 year period.

On studying the data in these histories, it is evident that some of the insulin which was added was for the purpose of maintaining a lower average blood sugar, and others for supporting a larger average diet, especially in carbohydrate, in order to promote the patient's well being. The 24 patients who began taking insulin during the 5 year period were taking an average of 30 units daily at the end of the period.

It is evident that, although the diabetes was progressive in some of the group, it was not by any means always so. In those requiring no increase in the amount of insulin and in those taking no insulin at the end of the period (45 in number), the diabetes certainly had not progressed noticeably. Of the patients whose insulin dosage was increased, a considerable number also had increases in diet.

*Infection.* In this investigation "infection" has been interpreted either as long-continued, chronic infection, or as repeated acute infections. These diagnoses were made in the wards or by other clinics to which the patients had been referred for examination and treatment (Table 4). According to this classification, 61% of these patients were found to have been free from infection, while 39% had infections during the 10 year period.

In Table 4 are shown the figures for the chronic infections found in these patients.

TABLE 4	
Infections	Incidence
Chronic pyelonephritis . . . . .	9
Chronic cholecystitis . . . . .	16
Tuberculosis . . . . .	9
Syphilis . . . . .	5

The acute infections were not common, and those usually found were pneumonia or abscesses. Acute sinus infections and acute appendicitis occurred occasionally. In a survey of the group, it was evident that some patients remained entirely free of infection, while others were subject to repeated infections of one kind or another. The acute infections often occurred in those patients who had also a chronic infection.

A comparison was made between the presence of infection and the age of the patient, the duration and the severity of the diabetes and

least strongly suggestive of an etiologic relationship between pernicious anemia and gastric carcinoma. We are not primarily concerned here with the mechanism of this relationship. Only a brief outline of the mass of evidence pertinent to this phase of the subject will therefore be considered.

A number of investigators have pointed out the tendency of patients with gastric carcinoma to develop anemia of macrocytic type, and have also considered this neoplasm a possible cause of true pernicious anemia. In the light of the classical work of Castle and his collaborators, this view was supported by the argument that destruction of the gastric mucosa by the tumor might lead to a loss of the "intrinsic factor," and could thus eventuate in pernicious anemia. However, attempts by a great number of other investigators to produce anemia in animals by the operative removal of the stomach and in some cases of portions of the small intestine as well have all led to failure. Similarly, very few patients among the great number annually subjected to gastrectomy ever develop true pernicious anemia. Thus, Doehring and Eusterman<sup>9</sup> report that follow-up examinations of 575 gastrectomized individuals yielded not a single case of pernicious anemia. Furthermore, the occurrence of pernicious anemia in patients with very small tumors which could scarcely destroy much of the gastric mucosa tends to refute this contention. It appears doubtful, therefore, that carcinoma of the stomach is a direct precursor of pernicious anemia.

The next possibility to be considered is that, conversely, pernicious anemia may be a precursor of gastric carcinoma. It is at once obvious that pernicious anemia *per se* can hardly be considered the main or the only cause of malignant gastric neoplasms, inasmuch as the latter occur far more frequently. However, there is almost no evidence to establish or refute the possibility that pernicious anemia may be only one, perhaps a very minor one, among several causes of carcinoma of the stomach. The literature of experimental cancer research is replete with examples of multiple causes of several varieties of cancer. It is therefore quite possible that the causes of gastric cancer are likewise multiple.

The final consideration is that a factor common to both conditions may be a precursor of both, or a concomitant of one and precursor of the other. Among the factors of this type which have been enumerated are gastritis, achlorhydria and achylia, constitutional and hereditary factors, and liver therapy for pernicious anemia.

Konjetzny<sup>22</sup> and others have been enthusiastic proponents of the thesis that chronic gastritis, particularly of the atrophic type, is a precancerous lesion. This view is based upon the frequent demonstration of gastritis and of proliferative mucosal changes in the vicinity of malignant gastric neoplasms. However, the recent careful studies of Guiss and Stewart<sup>14</sup> and of Hebbel<sup>17</sup> indicate that chronic gastritis occurs very commonly in individuals past middle age, and is no more frequently associated with gastric cancer than with malignancies primary elsewhere or with non-neoplastic diseases.

group there are 10 men, though in none of them was the enlargement more than minimal and no signs of hyperthyroidism were present in any of them.

*Liver.* The liver was palpable in 31% of this group, though in only 4 could it be considered a definite enlargement. No clinical symptoms of disease of the liver were found in any of these patients and no extensive studies of liver function were made.

*Gall Bladder.* The condition of the gall bladder is of interest in diabetes on account of its proximity to the pancreas and on account of the various attempts in the past to connect it with the etiology of diabetes. Of the 16 patients with gall bladder disease, there were 7 with gall stones, on 4 of whom successful cholecystectomies were done. The 3 remaining patients with a diagnosis of gall stones refused operation. However, they improved for a long time on low fat diets. The remaining 84 patients showed no evidence of gall bladder disease. The diagnoses of chronic cholecystitis and cholelithiasis were confirmed by cholecystogram.

*Anemia.* Examination for anemia was made by erythrocyte counts, and determinations of hemoglobin. These examinations showed that 74% of the group had more than 4,500,000 R.B.C. per cmm. and 14.5 gm. of hemoglobin per 100 gm. of blood. Of the 26 below these figures, only 3 had less than 4 million cells and 13.7 gm. of hemoglobin. It would seem that, on the whole, these patients maintained their blood in almost as satisfactory a condition as non-diabetics. Two patients with primary pernicious anemia are doing well under the combined treatment of both diseases. No significant differences were found in these patients compared with non-diabetics.

*Kidney Disease.* The incidence of kidney disease other than pyelonephritis has been variously reported from different clinics.<sup>3</sup> We have not made a complete study of the kidneys in this group of patients. However, 29 of them have shown albumin with casts in the urine on several examinations. These are present most frequently in the older patients in whom this finding might be expected. Of 25 patients below 41 years of age, only 2 have albumin in the urine. These are both men, 24 and 31 years old. One man and one woman in the 5th decade (both 48 years old) also have these findings. It would seem that nephritis is little, if any more, frequent in these diabetic patients than in non-diabetics within the same age limits.

Patellar and Babinski reflexes were found, during recent physical examinations, to be normal in 63% and absent in 15%. In the other 22% they were present, though diminished.

**Summary.** 1. A study is presented of 100 patients with diabetes of 10 or more years duration. The age and race distribution of these patients is that usually found in diabetes.

2. Observations on these patients show that diabetes does not always progress to greater severity. After comparing the diet and insulin at the beginning and at the end of a 5 year period, it is evident that the diabetes of 45% of the patients had not advanced. Ten of these patients required less insulin at the end than at the beginning

of the period. Of the 55 who required more insulin, a number had also received increases in diet.

3. Acidosis occurred in 3 of the group during the past 10 years.

4. While arteriosclerosis was present in a number of the patients, no amputations were done on any of them.

5. Anemia of a mild degree was present in 26 patients. However, only 3 had less than 4 million R.B.C. and less than 13.5 gm. of hemoglobin per 100 mg. of blood.

6. Chronic or repeated acute infections have been present in 39 patients. Of the former, cholecystitis (16 cases), pyelonephritis (9 cases), and tuberculosis (9 cases) were most frequently encountered.

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## DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

### II. CARDIAC STUDIES

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THE unusually high incidence of coronary sclerosis and its complications in diabetics, treated with high fat, low carbohydrate diet, as compared to non-diabetics is a well known clinical fact and has been attested by numerous pathologic studies.

This is not the place to enter into detailed discussion of the cause of arteriosclerosis in diabetes. Leary<sup>10</sup> states that excess cholesterol is the cause of the arteriosclerosis which is clinically significant, *i. e.*, sclerosis of the coronary, peripheral and cerebral vessels. Clinical study suggests that the degree of arteriosclerosis is in some way associated with the degree of hypercholesterolemia.<sup>2</sup>

The finding of a direct relationship between hypercholesterolemia and arteriosclerosis in diabetics suggested that the high incidence of the latter may have been due, to some extent at least, to the high fat content of the older diets. Nearly all available statistics are those obtained during the period preceding the high carbohydrate, low fat era. Joslin *et al.*<sup>9</sup> state that since the newer diets "the postponement of premature arteriosclerosis has already begun. No longer does the statement hold that premature arteriosclerosis can be found post-mortem in all cases of diabetes of 5 years duration." The purpose of this study is the determination of the status of the heart and aorta of patients who have been on the high carbohydrate low fat diet for at least 10 years.

*Material.* This study includes 100 patients, all of whom have been known to have diabetes for at least 10 years; the longest 27 years, the average duration was 13.7 years.

*Age:* The youngest patient was 14 years, the oldest 75 years. The majority, however, were between 50 and 70 years of age. Thirty-one were under 50 years of age and 69 were 50 years or older (Fig. 2).

*Sex:* Seventy-six were females and 24 were males. However, sex was more evenly divided in the group younger than 50, there being 13 males and 18 females. In the older group females predominated—58 to 11.

*Color:* There were 7 Negroes in the entire group and of these 6 were females. The remainder were white.

*Symptomatology.* Forty-five persons presented no cardiac complaints; 26 (57.8%) of the 45 were under 50 years of age and, of these, examination was entirely negative in 19. Only 19 (27.5%) of the older age group were free of symptoms, but only 4 of this group were negative on examination; 13 of the remaining 15 had slight or moderate hypertension.

The most common complaints were weakness and fatigue, which were present in 27 cases; palpitation was the main complaint in 13 instances. Seventeen patients had dyspnea, especially on exertion, and 4 of these complained of nocturnal dyspnea. In 3 of the latter patients, hypertension was marked, and in the 4th there was evidence of severe myocardial damage and marked enlargement of the heart. Edema of the ankles was present in 8 cases but in 4 there were marked varicosities which could account, in part at least, for the edema.

Eight had angina pectoris and 5 other patients had indefinite chest pain. All belonged to the older age group and of the 8 with angina pectoris there were 4 men and 4 women. The 5 cases with indefinite chest pain were women.

The history or ECG suggested that coronary occlusion had occurred in 4 instances, but definite electrocardiographic evidence was obtained in only 1. Two of the 4 cases had angina pectoris and are included in the group above.

*Hypertension.* Thirty-eight of the entire group had a systolic blood pressure of 160 or more.\* Examination of Figure 1 shows that all patients with hypertension were over 50 years of age, representing 55.1% of this group; there was not a single case under 50, and only 1 of the latter had a blood pressure over 150. The greatest incidence was found in the patients between 60 and 70 years, but the percentage increased with each decade (Fig. 2). Nineteen had a systolic blood pressure between 160 and 180, and 19 over 180; the highest recorded systolic pressure being 260. Only 3 (9.1%) of the 38 patients with hypertension were males, although men composed 18.6% of the group past 50; therefore, in this group hypertension was twice as common in females as in males.

\* Inasmuch as no case of a high diastolic pressure (100 mg. Hg or higher) was noted without an associated high systolic pressure, for purposes of simplicity and comparison with other similar studies, only systolic pressure will be discussed.



The orthodiagram disclosed cardiac enlargement in 10 of the 38 cases with hypertension; questionable enlargement in 4 and normal size in 24. In the 19 cases with systolic blood pressure over 180, 6 showed enlargement of cardiac area varying from 11 to 33%; 1 with questionable enlargement and in 12 cardiac area was within normal limits. The aorta was considered abnormal (dilated, elongated or calcified) in 16 patients. In the group with a systolic pressure of at least 180, the aorta in 9 was considered abnormal and in 10 normal. Seven of the 16 with abnormal aortas also showed cardiac enlargement, 7 normal sized hearts and 2 were questionable.

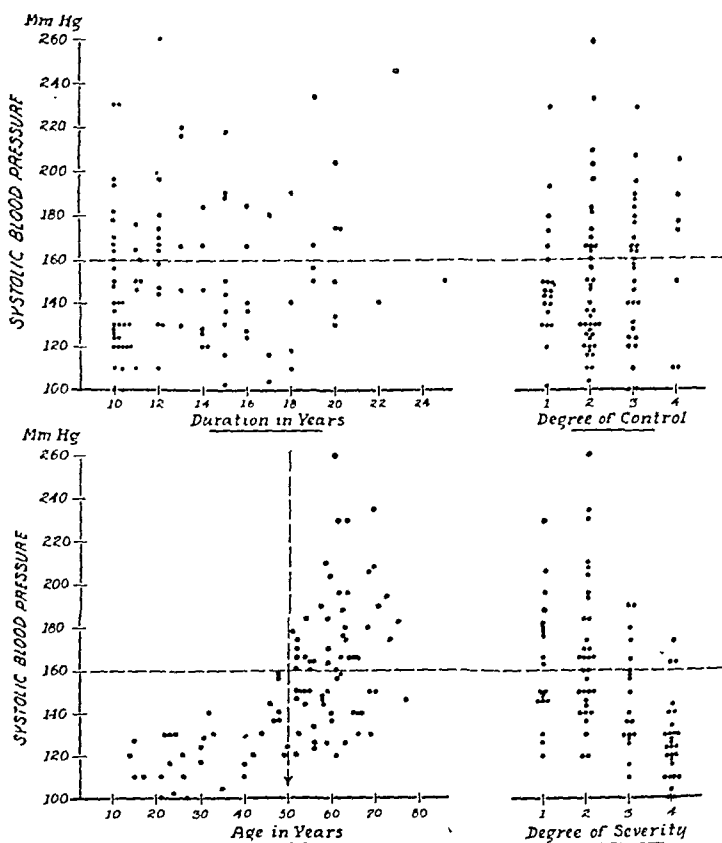


FIG. 1.—The influence of age, duration, severity and ability to control diabetes, upon the systolic blood pressure. The criteria for determining severity and ability to control the diabetic state are explained in Table 2 (page 4) in the first article of this series.

Examinations of the ECGs of the 38 cases failed to disclose a tracing of the type frequently associated with long standing hypertension. Inverted or diphasic T waves in Lead 1 were observed in only 2 cases, and in these the systolic blood pressure was 166 and 170. T waves less than 2 mm. in amplitude were observed in 7 cases; in 2 instances the systolic pressure ranged between 160 and 170, in 3 between 180 and 190, and in 2 over 190. Inversion of the T waves in one or more chest leads was present in 4 instances, the systolic pressures being 166, 170, 178 and 234.

*Electrocardiographic Changes.* Fifty-nine of the ECGs were normal except for left axis deviation or extrasystoles; normal ECGs were observed in 25 (80.6%) of the group below 50 years and 34 (49.3%) of those above 50 years.

*Arrhythmias:* Auricular fibrillation was observed in only 2 cases, 1 of these had exophthalmic goiter, the other rheumatic heart disease with mitral stenosis; both were in the older age group. The only other arrhythmia noted was ventricular extrasystoles, which was noted in 7 cases, but in only 2 were they numerous.

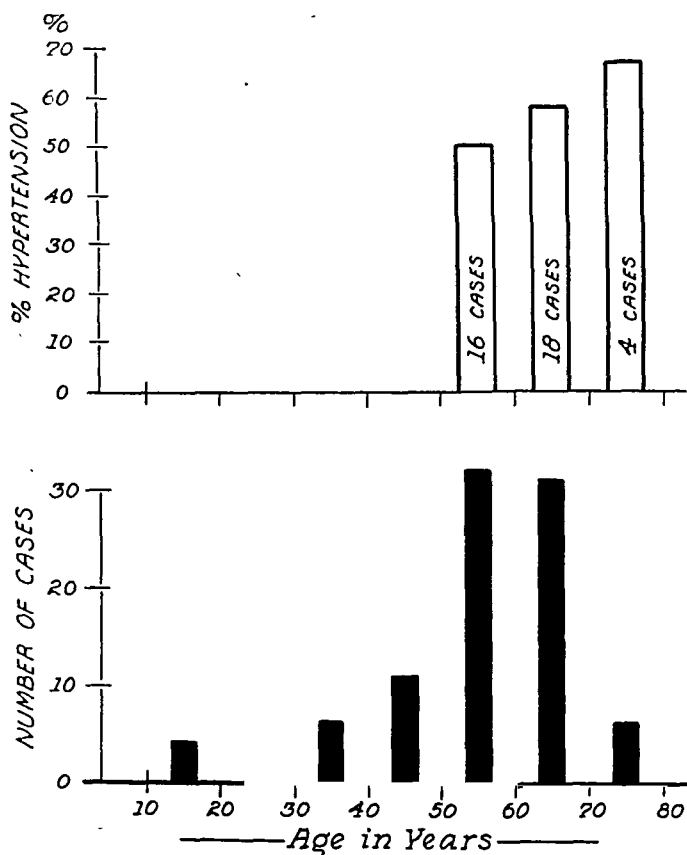


FIG. 2.—The age distribution of 100 cases of diabetes mellitus of at least 10 years' duration and the incidence of hypertension according to decades.

*QRS Complex Changes:* Two cases showed left bundle branch block and 4 marked intraventricular conduction defects. All were older than 50 years and 5 of the 6 patients had hypertension.

In 23 cases the QRS complexes were slurred in 2 or more leads; in 16 the slurring was slight, in 4 moderate and in 3 slurring was marked. One additional case showed splintering of the QRS complexes in Lead 1 and another in Lead 2.

*T Wave Changes:* Four cases showed T wave inversion in Lead 1 and in another the T wave was diphasic. In these 5 cases the T wave in CR-5 was also inverted. Six other patients showed inverted or

diphasic T waves in 1 or more chest leads. Two of the 6 were 23 and 15 years of age, the remainder were more than 50 years of age.

*Cardiac Size.* In determining cardiac enlargement, the tables of Hodges and Eyster<sup>7</sup> were used; cardiac area was considered normal if the computed area was plus or minus 10% of the predicted normal for height and weight. Cardiac area was within normal limits in 66 of the 100 cases; 9 were considered doubtful because the area was in the uppermost limit of normality. In 9 cases the area was smaller than average, the smallest being 28% below the predicted normal. In only 16 cases was cardiac area definitely above normal; the largest cardiac area was 54% above the predicted value. Only 3 of the 25 cases with enlarged or top normal hearts were under 50 years of age; 14 (56%) of this group of 25 had hypertension, although it is interesting that only 26.3% of the hypertensive group showed cardiac enlargement and 10.5% were doubtful. Five of the 6 cases with bundle branch block or severe intraventricular conduction defects showed cardiac enlargement of 16, 17, 20, 30 and 54%; in the other case cardiac area was normal.

*Aorta.* The ascending aorta was measured in one of the oblique views and the descending portion of the arch was measured by the Kreuzfuchs method. The limitations of both methods are appreciated, and the accuracy of the results obtained are therefore open to question. However, study of our material showed that in 24 the aorta was abnormal in that it was dilated and/or markedly elongated, or showed areas of calcification; in 76 the aorta could not be considered abnormal; although changes were observed in some they were commensurate with the age of the patient. All patients with abnormal aortas were older than 50 years of age, the percentage increasing with each decade and most (66.6%) had hypertension.

**Discussion.** Although the number of cases in this study is not large, and, as a result, deductions cannot be regarded as conclusive, nevertheless, certain observations merit discussion, namely:

(a) The infrequency of hypertension in the group under 50 years of age.

(b) In the group of 38 hypertensives, the comparatively low incidence of cardiac enlargement and the absence of ECG changes often observed in hypertension.

(c) The frequency of cardiac enlargement in patients (with or without hypertension) with definite ECG evidence of myocardial abnormality.

(d) The comparatively small number of patients in the younger aged group with evidence of cardiovascular abnormalities which could be attributed to diabetes. In most cases, with the possible exception of those in the younger age group, the available data does not permit a comparison of the cardiovascular status during the period the patients were on the two types of diet, consequently the influence, if any, of each upon the cardiovascular system cannot be differentiated.

(a) Bell and Clawson<sup>2</sup> considered that hypertension was about 2.7 times as common in diabetics as in non-diabetics and, among 175

patients examined postmortem at the Deaconess Hospital, Root and Sharkey<sup>13</sup> found 54% had had a blood pressure between 150 and 230. In our group of 100 cases, 38 had a blood pressure 160 or more; the highest being 260, and 10 others had a blood pressure between 150 and 160; therefore, 48% had a blood pressure over 150.

However, an examination of these cases disclosed certain interesting and pertinent facts. All cases of hypertension (160 mg. Hg) occurred in individuals past 50 years of age (Fig. 1), after which age the incidence increased with each decade and was twice as common in women than men. Figure 1 also suggests that the incidence of hypertension does not appear to be dependent upon the severity, control or duration of diabetes. The high incidence of hypertension in elderly diabetic females is striking, but the interesting observations of Arnett<sup>1</sup> show that hypertension is very common in elderly females; in an old ladies home 56 or 74.8% inmates between the ages of 62 and 95 had a blood pressure over 160 and, of these, 32 or 42.7% had a systolic blood pressure over 180. However, most observers state that hypertension is more common in diabetics than in non-diabetics, although Wilder<sup>16</sup> and also Donhoffer and Szabo<sup>4</sup> believe there is no difference in incidence. In 1929, Major<sup>11</sup> concluded that the blood pressure in diabetics was higher than in normal people of comparable ages, but the incidence of hypertension (150 mg. Hg) increased with age from 5.5% in the group between 35 and 40 to 77% in the group between 70 and 75. In the group between 40 and 45, 25.8% had a blood pressure over 150, and 29.9% in the group between 45 and 50. In our group the incidence increased with each decade (Fig. 2), but only 1 case under 50 years had a systolic blood pressure over 150. In Friedman's<sup>6</sup> series of 120 cases, permanent hypertension (over 150) was found in 30% of the group between 40 and 50 years. Although our group below 50 years comprised but 31 cases, the absence of systolic blood pressure readings over 160 and but a single case over 150, is significant, especially when compared with other series of diabetics who were treated with the older high fat, low carbohydrate diets. What rôle, if any, the high carbohydrate-low fat diet played in reducing the incidence of hypertension in the younger age group, however, is open to speculation.

(b) A comparison of ECG and fluoroscopic abnormalities in our group of hypertensives disclosed significant differences when compared to non-diabetic hypertensives. Various clinical studies upon the heart size in hypertension show that cardiac enlargement is present in at least two-thirds of all cases,<sup>16</sup> although methods of determining cardiac enlargement varies. In an unpublished study of 123 hypertensives (systolic blood pressure of 160 or over), including 10 with diabetes, 77 or 62.6% showed definite enlargement of cardiac area. In our group of 38 diabetics with a systolic blood pressure of 160 or over, only 10 (26.3%) showed enlargement of the cardiac area, 4 (10.5%) were doubtful, and 24 (63.2%) showed hearts of normal size. These figures suggest that cardiac enlargement in hypertension is twice as common in non-diabetics as in diabetics. The findings are apparently consistent with

those of Root and Sharkey,<sup>13</sup> who examined the postmortem records of 175 diabetic patients (treated by the older methods) at the New England Deaconess Hospital and found advanced coronary sclerosis in 60 of 93 cases with hypertension, but the striking feature was the lack of hypertrophy except in those cases with preëxisting hypertension.

Although significant changes are found in some of the ECGs of hypertensive diabetics, in none of the 38 cases was the ECG of the type frequently seen in long-standing hypertension and ascribed to left ventricular hypertrophy and by some to left ventricular strain. The 19 patients with a systolic blood pressure of 180 or more failed to show T-1 inversion, and some of these patients were known to have hypertension for a period of at least 10 years. The absence of the typical pattern of the so-called hypertensive ECG is consistent with the comparatively small number of hypertensives with cardiac enlargement compared to non-diabetics, although we are cognizant of the fact that hypertrophy may occur without enlargement of the cardiac silhouette. Although we have observed the hypertensive pattern in cases of hypertension in diabetics not included in this study, nevertheless it must be admitted that our group of 38 is too small to be conclusive and further study will be necessary before any definite conclusion can be drawn.

(c) All of the hypertensives were in the older age group, and in the majority the onset of diabetes was before the age of 50 and occurred in the high fat-low carbohydrate era—a period during which all clinical and pathologic studies attested to the frequency of arteriosclerosis in diabetes of 5 years duration, regardless of age. In the majority of cases there are no records of blood pressure readings during this period, but the available data indicates that in some, at least, blood pressure readings have shown a gradual elevation. It is highly probable, therefore, that in many cases arteriosclerosis preceded the hypertension, a sequence of events which Root and Sharkey believe may explain the absence of constant or marked hypertrophy in diabetic hypertensives. However, our data show a low incidence of ECG changes, indicative of myocardial abnormality in hypertensives without cardiac enlargement, and conversely a high incidence of cardiac enlargement in patients whose ECGs show definite evidence of myocardial abnormality with or without hypertension. In the majority of cases (64.7%) with definite electrocardiographic evidence of myocardial abnormality, with or without hypertension, the heart was enlarged or showed questionable enlargement, compared to 36.8% of the group of hypertensives. In only one of the latter was there evidence of severe myocardial abnormality in the ECG associated with a normal sized heart. Cabot<sup>3</sup> found 39% of 631 patients with uncomplicated arteriosclerosis to have cardiac enlargement, and although statistics obtained clinically cannot be compared accurately with those obtained from autopsy material, our data suggests the possibility that in diabetics, cardiac enlargement is frequently associated with arteriosclerosis. The low incidence of cardiac enlargement and

apparent arteriosclerosis in the younger group (under 50) with long-standing diabetes is strong suggestive evidence that present forms of treatment may be responsible for the reduction of premature arteriosclerosis, coronary disease and cardiac enlargement. The importance of adequate glycogen supply to the heart is well known, as is the fact the glycogen synthesis in the heart depends upon blood sugar concentration and insulin in the presence of sufficient oxygen. G. T. Evans<sup>5</sup> has demonstrated in the rat's heart that, by increased insulin and glucose, the normal values of glycogen may be increased so that the heart becomes its own storehouse. One may, therefore, speculate as to whether in the human the high carbohydrate diet with insulin may not also augment the glycogen content and, if given before the advent of advanced sclerosis, increase cardiac efficiency so as to prevent undue left ventricular strain in the presence of hypertension.

(d) The comparatively small number of patients under 50 (average age 31.7 years) with cardiac abnormalities which could be attributed to their diabetic state appears significant. Although the duration of diabetes in this group was 10 to 22 years (average 12.9 years), 24 (77.4%) of the 31 cases showed no definite evidence of disease of the heart or aorta clinically, orthodiagraphically or electrocardiographically. Included in the group of abnormal cases are 3 with rheumatic heart disease and 1 case of doubtful etiology. The 3 patients (9.7%) with cardiac abnormalities which could be attributed to their diabetic state, were aged 24, 30 and 47 years with diabetes of 15, 16 and 15 years duration, respectively. Another patient, a woman of 43 years with diabetes of 22 years duration, is known to have peripheral vascular disease; therefore 4 (13%) of the 31 cases under 50 years have cardiovascular abnormalities which could be attributed to their diabetic state. On the older diets, Shepardson<sup>14</sup> found 36% of 50 cases with an average age of 23.4 years with diabetes of at least 5 years duration to have cardiovascular disease, and Rabinowitch<sup>12</sup> stated 80% of patients with diabetes of 5 years or more, regardless of age, had cardiovascular disease.

All studies indicate the high incidence of angina pectoris and/or coronary occlusion in diabetes. Our study also shows a high incidence—11.6% of the group over 50 and 8% of the entire group—but it is worthy of note that the age and the ratio of men to women (5 to 1) in the older age group is comparable to that of the non-diabetics with angina pectoris. However, the number of cases of angina pectoris and/or coronary occlusion is not sufficiently large to be conclusive.

**Summary and Conclusions.** 1. The cardiovascular status of 100 diabetics who have been on a high carbohydrate-low fat diet for at least 10 years was studied. Sixty-nine of this group were over 50 years of age, and 31 under 50.

2. Hypertension (systolic blood pressure 160 mm. Hg) was present in 38% of the cases. All cases with hypertension were past 50 years of age; the incidence increased with each decade and was twice as common in women as men. The incidence of hypertension apparently was not dependent upon duration, control or severity of the diabetes.

3. Cardiac enlargement was present in 10 of the 38 cases with hypertension, 4 were doubtful and 24 showed hearts of normal size. This incidence of cardiac enlargement is about one-half that observed in non-diabetic hypertensives.

4. The greatest degree of cardiac enlargement was observed in cases with ECG evidence of myocardial abnormality (with or without hypertension), and conversely there was a low incidence of ECG changes indicative of myocardial abnormality in the hypertensives without cardiac enlargement.

5. An ECG of the type frequently seen in hypertension and ascribed to left ventricular hypertrophy or to left ventricular strain was not observed in any of the 38 cases with hypertension.

6. Only 3 (9.7%) patients under 50 had abnormalities of the heart which could be attributed to their diabetic state. The 3 patients were aged 24, 30 and 47 years with diabetes of 15, 16 and 15 years, respectively.

7. The low incidence of cardiovascular abnormalities in the younger group compared to similar studies in the literature on a high fat-low carbohydrate diet is suggestive evidence of the value of the high carbohydrate-low fat diet in reducing the incidence of premature cardiovascular abnormalities.

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## DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

### III. OCULAR FINDINGS

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THIS report concerns examination of 100 diabetic patients who have been carefully observed for a period of 10 or more years. These patients were under the care of Dr. Russell Richardson, Chief of the Metabolic

Division of the University Hospital and his staff. They were chosen by the Diabetic Staff for their ability to coöperate in their treatment.

The care and therapy of these patients has been described in the paper of Drs. Richardson and Bowie<sup>1</sup> and will not be repeated.

**Method.** At the end of 10 years of adequate Out-Patient Department treatment, the eyes of these patients were carefully examined and the following examinations were made:

1. *Visual Acuity* with best possible correction; patients under 45 years received a cycloplegic refraction; those above 45 years a manifest refraction.
2. *Extra-ocular Movements*—for paralysis of individual muscles and conjugate movements.
3. *Pupils*—for reaction to light and accommodation.
4. *Cornea*—(a) For wrinkling of Descement's membrane.  
(b) Pigment deposition on posterior surface.
5. *Iris*—for depigmentation and signs of old iritis.
6. *Lens*—for opacities, employing a slit-lamp, all pupils were fully dilated and examined for:
  - (a) Anterior cortical spicules or spokes.
  - (b) Posterior cortical spicules or spokes.
  - (c) Subcapsular flaking, anterior or posterior.
  - (d) Nuclear sclerosis.
  - (e) Fissures of anterior or posterior cortex.
7. *Intra-ocular Tension*—wherever questionable a tonometer was used.
8. *Retina*—was scrutinized for:
  - (a) Punctate and superficial hemorrhage.
  - (b) Exudates of waxy or cotton wool type.
  - (c) Vessels were examined for any sign of sclerosis or hypertension.
9. *The Optic Nerve*—was viewed with atrophy and neuritis in mind. Any questionable case had a peripheral and central field with white and colored test objects.

These structures were examined because they have been shown by Waite and Beetham<sup>6</sup> to reveal the most frequent abnormalities in diabetic eyes.

TABLE 1.—COMPARISON OF INCIDENCE OF OCULAR FINDINGS IN DIABETICS AND NON-DIABETICS

	This series (%)	Waite and Beetham's diabetic patients (%)	Waite and Beetham's non-diabetic patients (%)
Wrinkles in posterior layer of cornea . . .	8	26.0	10.5
Corneal pigmentation of posterior surface . .	16	11.8	5.7
Depigmentation of iris epithelium . . .	7	6.0	2.0
Iritis . . . . .	1	1.3	1.3
Tension . . . . .	1	0.5	
Pupil reactions sluggish to light . . .	4	2.8	3.5
Extra-ocular muscle palsies . . . . .	5	4.0	0.1
Optic atrophy . . . . .	1	0.6	0.4

Waite and Beetham<sup>6</sup> reported a comparative study of 2002 diabetics and 457 non-diabetics. Their diabetic patients varied widely in age and in the duration of the disease. Although therapy was administered to all of their patients, many patients were examined either shortly before or shortly after treatment had been started. The findings they presented may therefore be used to express the incidence of ocular findings in diabetics who have not necessarily been controlled for any



definite period. Thus, their data can be compared to the results of this series of diabetics that has been closely observed and treated for 10 years, and will be a relative means of evaluating the effect of this form of therapy. (See Table 1.)

In reviewing Table 1 it is evident that there is little variation between these 10-year treated diabetics and the cases reported by Waite and Beetham. The one major exception is the wrinkling in the posterior layer of the cornea, the incidence in the 10-year treated cases being much less than in Waite and Beetham's cases. Corneal pigmentation still remains greater, in spite of 10 years of therapy, than in the non-diabetic. This is the same for depigmentation of iris epithelium. There was no greater incidence of iritis, of increased intra-ocular tension, sluggish pupils, nor optic atrophy. It is worthy of mention that in the 24 cases with clinical evidence of pains in the extremities, not one showed evidence of either optic or retrobulbar neuritis. The incidence of extra-ocular muscle palsies was greater in this 10-year treated group, but every one of those cases had a history of onset of palsy prior to the starting of 10-year therapy.

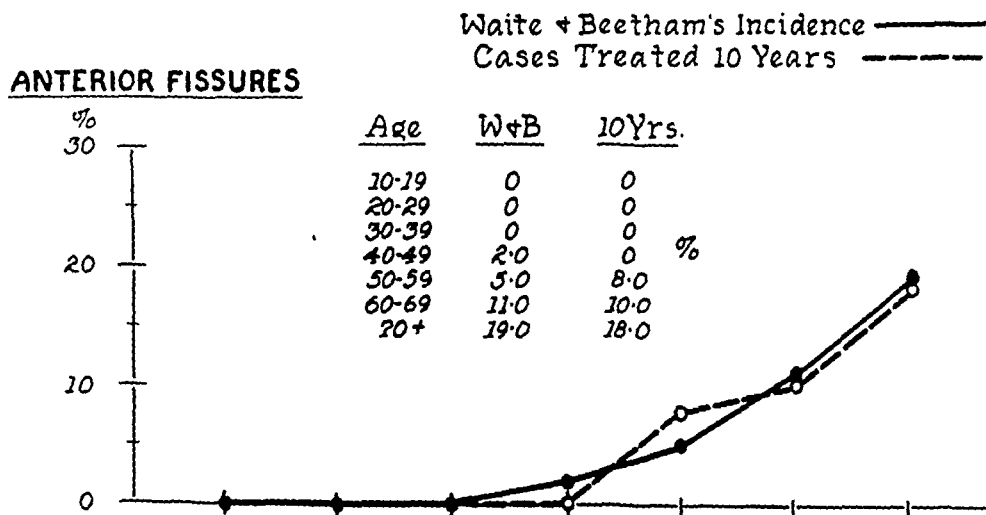
Andersen,<sup>1</sup> in 1925, and Gradle,<sup>2</sup> in 1926, published statistics as to the incidence of lens changes in the population at large after 40 years of age. (See Table 2.) The incidence of spicules, punctate spots, fissures, nuclear sclerosis, and all opacification of lens except sub-capsular flocculi in the 10-year group showed a striking similarity to Gradle and Andersen's figures.

TABLE 2.—INCIDENCE OF LENS AND RETINAL CHANGES

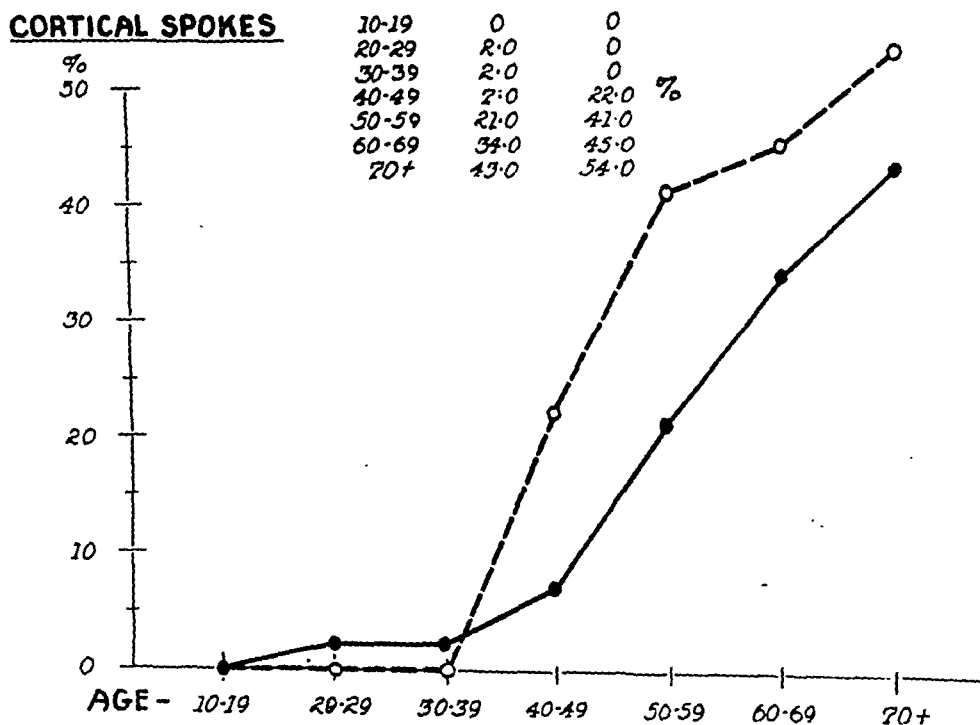
Incidence of lens changes				Incidence of retinal changes in relation to grade of sclerosis		
Decade	Andersen (%)	Gradle (%)	This series (%)	Grade	Retinal changes	
					Punctate retinal hemorrhages (%)	Exudates (%)
41-50 . . .	38.2	34.1	33	0 . . . . .	4.5	9
51-60 . . .	65.0	66.2	70	1 . . . . .	36.0	26
61-70 . . .	85.0	68.4	79	2 . . . . .	41.0	36
70 up . . .	92.0	90.0	90	3 . . . . .	50.0	40
				4 . . . . .	100.0	100

Anterior cortical spokes and spicules of the 10-year treated series can be compared with the diabetics of Waite and Beetham. The same thing can be done with fissures. A glance at these 2 graphs (1 and 2) shows that the fissures in all instances are strikingly parallel, whereas anterior cortical spokes are slightly greater in the 10-year cases. In analyzing this fact, it is wise to remember that Waite and Beetham's figures are based on 4001 diabetic eyes, more than 50% of which were of less than 5 years duration, while in this series all cases have gone over 10 years. The graph, therefore, indicates a greater incidence of anterior cortical spokes in 10-year cases than in those of shorter duration. Waite and Beetham have already shown this fact that spokes in diabetics increase with duration of diabetes and that, in their cases of 10 to 15 years duration, 27% showed anterior cortical spokes. In

these cases, all over 10 years, 32% showed anterior cortical spokes. It can, therefore, be stated that the treatment this group has received has not significantly altered the incidence of anterior cortical spokes.



GRAPH 1.—Incidence of anterior fissures. The data in Graphs 1 to 6 are compared to those of Waite and Beetham.<sup>2</sup>



GRAPH 2.—Incidence of cortical spokes.

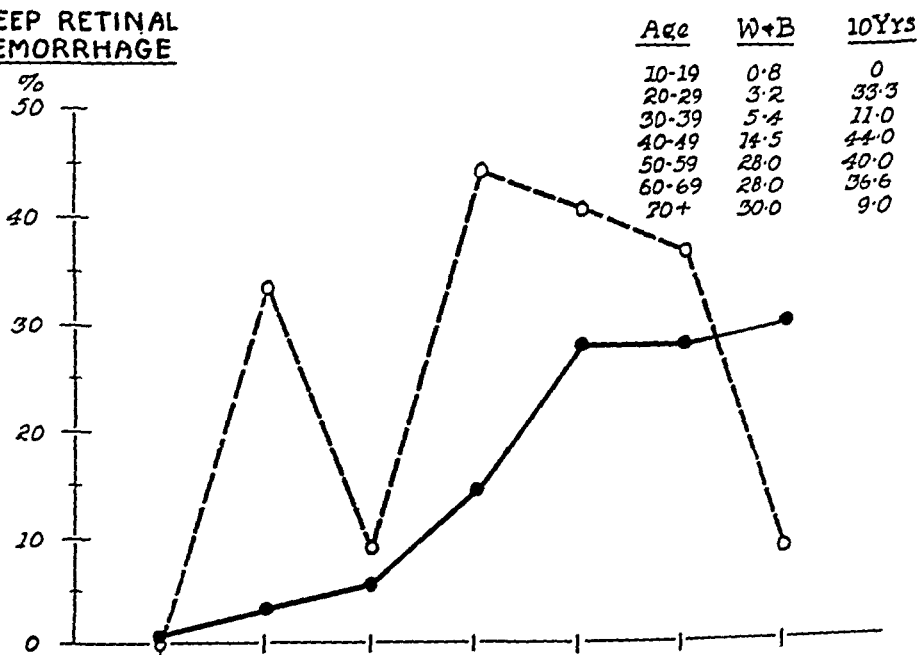
A similar approach for posterior cortical spokes led to the same conclusion.

The incidence of subcapsular flocculi was 5% in this series. O'Brien,

Molsberry and Allen<sup>3</sup> found 12 snow-flaked cataracts in 126 patients, approximate incidence 10%. They concluded that poorly controlled diabetes, especially if severe and prolonged, was the rule in these cases. This would seem to indicate that therapy has helped to reduce the incidence of the so-called typical diabetic cataract. Likewise, in Waite and Beetham's cases, many of which were of shorter duration than 10 years, and most of which had some form of therapy for varying lengths of time, the incidence of flocculi cataracts was 4%. It would, therefore, seem that therapy tends to reduce the incidence of sub-capsular flocculi, not to eliminate it entirely. It may also be that therapy prevents progression of flocculi in some cases. In this series, the incidence of nuclear sclerosis showed no striking variation from incidence of sclerosis in the non-diabetic. There was 1 case of complicated cataract in this series, while Waite and Beetham had 6%; therapy might have reduced the incidence.

Waite + Beetham's Incidence —————  
Cases Treated 10 Years - - - - -

# DEEP RETINAL HEMORRHAGE



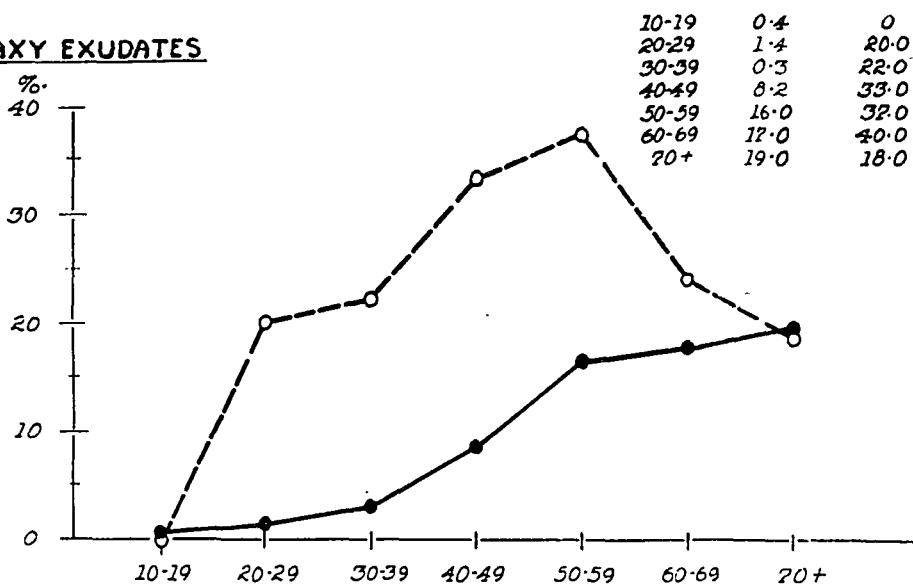
GRAPH 3.—Incidence of deep retinal hemorrhage.

Sclerosis of retinal vessels showed a striking similarity in incidence in the 10-year cases to Waite and Beetham's reported diabetics. It is well to remember that Waite and Beetham's diabetics had sclerosis practically identical in grade and kind to a control series of non-diabetics. It is possible to compare the figures of this 10-year group with those of Waite and Beetham as the sclerosis was graded according to their suggested plan.

Graphical comparison may be employed in studying the fundus

changes. (See Graphs 3 and 4.) Realizing that Waite and Beetham's figures are based on cases, more than 60% of which were less than 5 years' duration, the seemingly greater incidence of punctate hemorrhages in the 10-year treated group may be simply a confirmation of a fact prevalent in the literature that hemorrhages tend to increase with duration of diabetes. However, in addition to their findings recorded in Graph 3, in cases of 10 to 15 years' duration; Waite and Beetham have shown that the incidence of deep punctate hemorrhages was 43%, and the average age of the group was 43 years. The incidence of deep retinal hemorrhages in 10-year treated cases was only 31%, and the average age 53 years. It would seem, therefore, that although the therapy used here has not eliminated hemorrhages, it has reduced them. This same analysis can be applied to exudates.

### WAXY EXUDATES



GRAPH 4.—Incidence of waxy exudates.

Further findings obtained from this series may be of value in considering the question of specificity of diabetic retinopathy. Analyzing the incidence of punctate hemorrhages according to grade of sclerosis, it is evident that as the sclerosis increases the hemorrhages and exudates increase. (See Table 2.) On the other hand, it is known that arteriosclerosis in the non-diabetic produces less than 5% of punctate hemorrhages at any age, so that arteriosclerosis is not the sole etiologic factor.

There were 20 patients in this series that showed no hypertension, no ECG evidence of myocardial damage, no albumin, casts, or R.B.C. on urinalysis, and no cardiac findings on physical examination. In spite of this, 5 of them, or 25%, showed punctate hemorrhages. Other factors which could be evaluated in this series were:

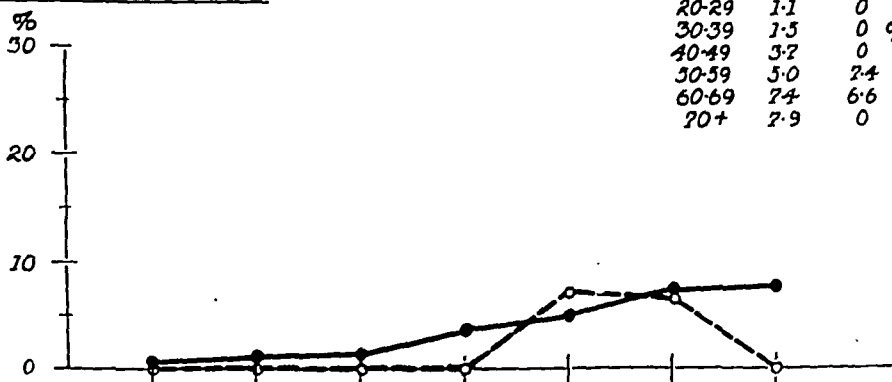
(a) Sixteen patients out of 31, or 52%, with blood pressures of above 150 systolic and/or 90 diastolic, failed to show punctate hemorrhages.

(b) Ten patients out of 21, or 47%, with evidence of renal damage by albumin or casts or R.B.C. failed to show punctate hemorrhages.

(c) Twenty-three patients out of 40, or 57%, showing any form of sepsis ranging from furuncle to tuberculosis, failed to show any punctate hemorrhages.

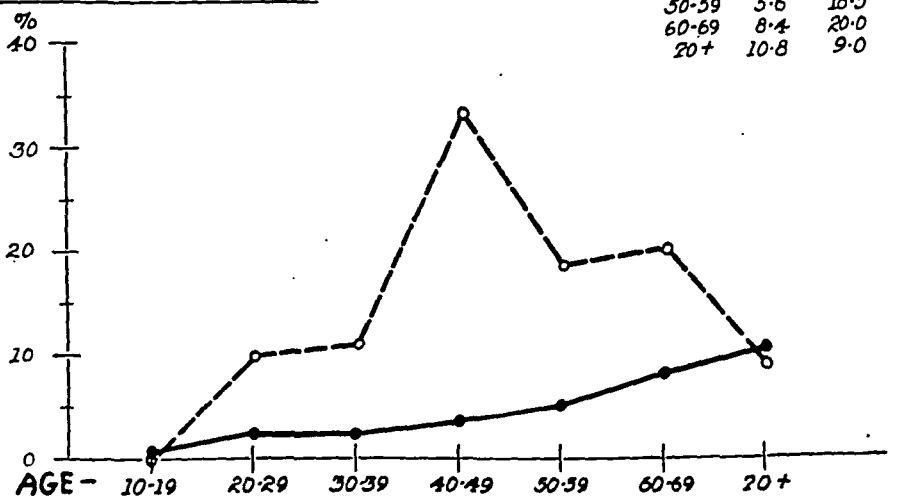
Waite + Beetham's Incidence —————  
Cases Treated 10 Years - - - - -

### COTTON-WOOL EXUDATES



GRAPH 5.—Incidence of cotton-wool exudates.

### SUPERFICIAL HEMORRHAGE



GRAPH 6.—Incidence of superficial hemorrhage.

These findings may indicate that, although arteriosclerosis, sepsis, renal damage and hypertension contribute to the production of retinal hemorrhages, they are not the basic etiologic factor.

Of 20 patients showing superficial hemorrhages; all showed at least Grade 2 sclerosis, only 2 showed no evidence of hypertension, renal damage, and had blood sugar levels below 150 mg. %.

According to the accompanying graphic comparison (see Graphs 5 and 6), cotton-wool exudates were similar in incidence to those of Waite and Beetham's, while the superficial hemorrhages showed a greater incidence in the 10-year treated cases.

In this series, there were 3 cases of retinitis proliferans. This is a trifle greater than the incidence in the general population.

No varices were observed in this group; incidence reported by O'Brien and Allen<sup>4</sup> was much less than 1%.

**Summary.** The following points may be noted:

1. Closely controlled therapy has apparently reduced the incidence of corneal wrinkles in the diabetic.

2. Increased motility of pigment found in the diabetic has not been affected by this form of therapy and there is no significant difference in the incidence in the treated diabetic and in the non-diabetic of iritis, muscle palsies, optic neuritis, optic atrophy, or of the senile type of lens changes.

3. Complicated cataracts are apparently fewer in 10-year treated diabetics than in the untreated.

4. Subcapsular "snow-flake" cataracts are still found in the 10-year treated diabetic.

5. The 10-year treated diabetic has an incidence of sclerosis similar to the non-diabetic and to the diabetic of varying duration and therapy.

6. Deep retinal hemorrhages and exudates increase with the duration of diabetes, and may be slightly decreased by closely observed therapy.

7. Although arteriosclerosis, hypertension, renal disease, sepsis, hyperglycemia, may all influence the incidence of deep punctate hemorrhages and waxy exudates, no one of them is the basic etiologic factor.

8. Increased superficial hemorrhages can be expected with increased duration of diabetes even under closely observed therapy.

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### DIABETES MELLITUS AS OBSERVED IN 100 CASES FOR 10 OR MORE YEARS

#### IV. PERIPHERAL VASCULAR FINDINGS IN 89 OF THESE CASES

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It is well known that patients with diabetes mellitus are predisposed to arterial disease and occlusion in the extremities. Gangrene and amputation have been frequent complications in diabetic patients. As

part of a study carried out by Richardson and Bowie,<sup>8</sup> Edeiken,<sup>2</sup> and Leopold,<sup>5</sup> 89 of their patients who had diabetes mellitus for 10 years or longer were studied to determine the degree of peripheral vascular disease present. These patients were under reasonably good modern treatment, the majority of them from the Diabetic Out-Patient Department of the Hospital of the University of Pennsylvania. They had been on relatively high carbohydrate diets and the degree of control can be seen in Table 3.

*Method.* A complete history was taken relating to possible symptoms of peripheral vascular disease in the extremities. The patient was questioned regarding pain, coldness, cyanosis, numbness and tingling, edema, phlebitis, cramps in the legs, ulcers and intermittent claudication. The amount of tobacco used was noted.

The physical examination included the blood pressure reading and palpation of the dorsalis pedis, posterior tibial, radial and ulnar pulses. Rapidity of color changes and venous emptying were observed on elevating the legs for 1 minute and then observing the rate of flushing and venous filling when the legs were held in the dependent position. Oscillometric records were obtained at the ankles with a recording oscillometer. The presence of lesions such as ulcers or gangrene was recorded. A reflex vasodilatation test was done where the clinical examination suggested reduction in blood flow. A histamine test was done in a few patients. Roentgen examination for calcification of arteries in the legs was not done.

Evaluation of the degree of arterial occlusive disease present was based on the above studies. Those with actual reduction in blood flow and severe symptoms or lesions were considered severe. Those with reduction in blood flow and with moderate or slight symptoms were considered moderate; those with missing pulses but no reduction in blood flow were considered slight.

*Results.* Thirty-three of the 89 patients (37%) had evidence of arteriosclerotic occlusive disease (Table 1). In 21 of these the arterial disease was slight, in 9 moderate, and in 3 severe. Five of the 33 were males (15%). Although in the entire group the number of female patients was only 3 times the number of males (67 females [75%], 22 males [25%]), there were more than 5 times as many female patients in the group with peripheral arteriosclerotic disease (28 females [42%], 5 males [22%]). On the other hand, in a representative series of arteriosclerotic patients without diabetes in the Peripheral Vascular Clinic only about one-seventh (14%) were females. The diabetic state, therefore, appears to have played a part in the production of arteriosclerosis, particularly in the female patients of this group.

When one considers the group of 32 patients who were under 50 years of age, there were only 3 (11%) with evidence of arteriosclerosis in the legs; slight in 2, and moderate in 1. In the patients under 50, there was a low incidence of arteriosclerosis not only in the legs but in the heart and eyes (Edeiken<sup>2</sup> and Leopold<sup>5</sup>). This compares with an incidence of arteriosclerosis in 85% of 81 patients under 50 who had been treated by older methods (Rabinowitch).<sup>6</sup> Our own findings in the patients under 50 indicate that premature arteriosclerosis is much less in this series. Rabinowitch<sup>6</sup> reports another group of 28 patients under 50 years who had been treated with high carbohydrate diets in whom arteriosclerosis was found in only 11 or 39%.

TABLE 1.—ANALYSIS OF PERIPHERAL VASCULAR CHANGES IN PATIENTS WITH DIABETES FOR 10 YEARS OR MORE

Age group (yrs.)	No. of patients	Symptoms of arteriosclerotic peripheral vascular disease in legs				Pulses missing in legs				Oscillometric reading				Grade of arteriosclerotic peripheral vascular disease			
		None			Severe	One pulse missing	More than one pulse missing	Normal	Reduced		Severe	None	Slight	Mod.	Severe		
			Slight	Mod.					Slight	Mod.							
10-19	4	4	..	..	..	..	2*†	6	3†	1*	..	4					
20-29	10	10	..	..	..	1	2	6	2	..	..	7					
30-39	8	8	..	..	..	2	..	7	1	2†	..	8	1				
40-49	10	8	2†	..	..	4	5	14	7	3	3	17	7	1			
50-59	27	21	2	3	1	1	7	12	7	5	2	13	9	2		2	
60-69	25	19	1	5	..	..	3	..	2	1	2	..	3	1		1	
70-79	5	1	1	2	1	..	—	—	—	—	—	—	—	—		—	
	—	71	6	10	2	8	19	45	22	12	7	56	21	9		3	
												Total					
	Female	67															

\* Thrombo-angiitis obliterans.

† Arterial spasm in 1 patient.

‡ Arterial spasm in 3 patients.



TABLE 2.—RELATIONSHIP BETWEEN DEGREE OF ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE AND SEVERITY OF DIABETES

Arteriosclerotic peripheral vascular disease		Severity of diabetes in terms of amount of insulin required			
Degree of severity	No. of patients	No insulin	Up to 25 units	Up to 50 units	Above 50 units
None	56	6	18	12	20
Slight	21	7	7	3	4
Moderate	9	1	3	5	
Severe	3	1	2		
Female—67					
Male—22					
Total—89					

TABLE 3.—RELATIONSHIP BETWEEN DEGREE OF ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE AND CONTROL OF DIABETES

Arteriosclerosis		Control of diabetes in terms of average height of blood sugar			
Degree of severity	No. of patients	140 mg. or less	140 to 180 mg.	180 to 250 mg.	Over 250 mg.
Slight	21	4	7	6	4
Moderate	9	1	2	5	1
Severe	3	..	3	—	—
Total	33	5	12	11	5
No arterio-sclerosis	56	17	25	15	4

The data in Table 2 indicate that the severity of the diabetes did not affect the degree of arteriosclerosis. The 3 severe vascular cases were all milder diabetics.

The data on the effect of control of the diabetes disclosed a greater percentage with arteriosclerosis who have poor control of the diabetes. In measuring the control of diabetes by the level of blood sugar it should be noted that most of the patients were free of glycosuria. Sixteen (46%) of 35 patients not well controlled (blood sugars over 180 mg.) had peripheral arteriosclerosis, as compared with 18 (33%) of 54 patients who were well controlled (blood sugars under 180 mg.) See Table 3.

Although small necrotic lesions were present in 3 patients, there were no amputations. It is worth noting that this group of 89 patients have had diabetes mellitus for periods ranging from 10 to 25 years without a single patient requiring amputation of a toe or leg. This is at least partly the result of modern emphasis placed on the care of the feet. A great many of the patients had been examined prior to the present study purely to evaluate the peripheral vascular status and to instruct them on the prophylactic care of the feet.

Another finding in the study was the absence of knee or ankle jerks and impaired vibration sense in 31 of the 89 patients. There was evidence of arteriosclerotic occlusion in 24 of these 31 patients. Dry and Hines<sup>1</sup> point out the relationship between lesions of the arterioles and neuritis in the diabetic. They believe that the neuritis is due to involvement of the vasa nervorum.

**Comment.** The findings in the group of patients studied, confirm those in other reports<sup>3,4,7</sup> that constant and adequate control of the diabetic with insulin and relatively high carbohydrate diet tends to prevent premature arteriosclerosis. Arteriosclerosis, when it does occur in the well-controlled diabetic, does so at the age when it is also found in non-diabetics. Furthermore, the modern handling of arteriosclerosis in the legs has reduced amputations in diabetic patients. This is due to a number of factors, among which one must mention not only adequate control of the diabetes and prophylactic care of the feet but also the use of sulfonamides. The latter group of drugs has greatly reduced the need for amputating a leg in a diabetic patient because of infection.

The effect of modern treatment on the incidence of arteriosclerosis in the diabetic is not completely evident in the patients past 50. Many of the older patients were on high fat diets at the onset of their disease. Furthermore, many patients do not stay under constant control. A lapse of several months in proper treatment may cause arterial changes which are irreversible (Rabinowitch<sup>7</sup>).

**Summary.** A group of 89 patients with diabetes mellitus from 10 to 25 years, under reasonably good treatment, were studied from the standpoint of arteriosclerotic occlusive disease in the legs. Three patients (11%) of those under 50 years of age, and 30 (34%) of those over 50 had evidence of peripheral arteriosclerosis.

Premature arteriosclerosis (below 50) was, therefore, not common in this group of patients. The severity of the diabetes did not affect the incidence of arteriosclerosis. The adequately controlled patients had a smaller incidence of arterial disease. Of the females, 42% had arteriosclerotic occlusive disease, as compared with 23% of the males.

There were no amputations in the entire group. Neuritis in the extremities was present in 31 of the 89 patients, chiefly in those with arteriosclerosis.

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**Final Summary of Series of 4 Articles.** 1. In the 4 preceding papers is presented a study of 100 patients with diabetes mellitus of 10 or more years' duration controlled by insulin and measured diets.

2. Observations show that in at least 45% of them the severity of the diabetes did not progress.

3. Neither the duration nor the severity of the diabetes appears to influence the incidence of hypertension, infection, or ocular sclerosis. However, prolonged diabetes appears to increase the incidence of deep

retinal hemorrhages and exudates and superficial hemorrhages in the eyes.

4. The incidence of cardiac enlargement in those patients who had hypertension is about one-half that observed in non-diabetic hypertensives.

5. In our patients under 50 years of age the incidence of cardiovascular disease was lower than that previously found in diabetics.

6. Arteriosclerotic occlusive disease of the lower extremities was found in 46% of the women examined and in 22% of the men. This much higher incidence in diabetic women than in women without diabetes parallels the greater frequency of coronary vessel disease in diabetic as compared with non-diabetic women.

R. R.

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## GELATIN AS A PLASMA SUBSTITUTE

### THE EFFECT OF GELATIN INFUSION ON THE SUBSEQUENT TYPING AND CROSS-MATCHING OF THE BLOOD, WITH A METHOD OF ELIMINATING THE PHENOMENON OF PSEUDOAGGLUTINATION

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EARLY in the course of studies on gelatin as a plasma substitute, it was observed that the addition of gelatin to blood, either *in vitro* or *in vivo*, causes a definite acceleration in the rate of sedimentation of erythrocytes. This phenomenon is associated with the formation of aggregates of long and short, compact rouleaux, and has been referred to by Ivy<sup>1a</sup> under the term "pseudoagglutination." The phenomenon of hemagglutination of erythrocytes by gelatin was first described by Karsner and Hanzlik<sup>2</sup> in 1920. Ivy and his collaborators<sup>1a</sup> recognized its occurrence in dogs after gelatin infusions and noted that a 10% dextrose solution decreased the amount of pseudoagglutination *in vitro*. We have previously reported on the effects in dogs of pseudoagglutination in relation to prolongation in clotting time and increase in the sedimentation rate.<sup>6</sup> Parkins<sup>5</sup> has shown that there is no change in oxygen saturation of dog erythrocytes after gelatin infusion, in spite of pseudoagglutination. Vogelaar<sup>7</sup> has demonstrated the effects of pseudoagglutination of erythrocytes on the sedimentation rate in man and has shown that addition of glycine to gelatin-blood mixtures alters the pseudoagglutination and prevents the increase in sedimentation rate.

Since gelatin is enjoying increasing use as a plasma substitute in the prevention and treatment of shock, and since many patients receiving gelatin may subsequently require transfusions of whole blood

for correction of anemia, it becomes important to determine whether pseudoagglutination interferes with the accurate performance of blood-typing and cross-matching. Actually, this has not emerged as a problem of any importance in connection with our own clinical studies on the use of gelatin;<sup>3</sup> nor have we observed that pseudoagglutination of erythrocytes in any way limits the tolerance of patients for gelatin. However, a recent statement on gelatin by the Sub-committee on Blood Substitutes of the National Research Council alludes to possible difficulty with the typing of blood of patients after gelatin infusion;<sup>4</sup> therefore, it seemed necessary to obtain further information on this subject. The present report is based on experiments which we believe will serve to clarify the problem.

**In Vitro Procedure.** Oxalated blood of each of the 4 Landsteiner groups A, B, AB and O was mixed with 4% gelatin solution,\* to give concentrations of gelatin in whole blood of 20%, 40%, 60% and 80% respectively. This is equivalent to 0.8 to 3.2 gm. of gelatin per 100 cc. of whole blood. The mixtures of gelatin and whole blood were allowed to stand with frequent mixing for periods ranging from 10 to 30 minutes.

Each of these specimens was then typed, using A, B and O typing sera with saline suspensions of erythrocytes taken from the gelatin-blood mixtures. The reactions were studied under the microscope.

**In Vitro Observations.** In none of the serum-erythrocyte mixtures was there any difficulty in typing. There was nothing in the way of pseudoagglutination, even in the higher gelatin concentrations, which could be considered to be confusing. The only microscopic evidence of pseudoagglutination was the occasional appearance of compact rouleaux of 4 or 5 cells which were never seen in greater number than 4 to 5 areas per low-power field. None of these could possibly be confused with actual agglutination.

No interference with expected agglutination was encountered. No difference was noted between sparse and dense suspensions of cells.

The typing of blood of all groups was in no way affected by the addition of solutions of either 5% glucose in water or 1% glycine in physiologic saline to the serum-erythrocyte preparations.

**In Vivo Procedure.** Following single and repeated infusions of 6% gelatin solutions (Knox P-11-20) in quantities of 500 and 1000 cc. per infusion, to a maximum total of 3500 cc. in 4 days, blood grouping, and cross-matching was repeatedly done at varying intervals after gelatin infusion on 10 patients.

Blood samples were drawn over time intervals varying from immediately after to 72 hours after infusion. Several blood samples were taken from patients while gelatin was being administered.

Each sample was typed and cross-matched with from 1 to 3 other blood samples from patients who had not received gelatin. Each serum-erythrocyte mixture was prepared in 3 ways: first with serum and erythrocytes only, second with the addition of 5% glucose in water, and, finally, with the addition of 1% glycine in physiologic saline to the serum-erythrocyte mixture. The latter 2 experimental procedures were done by 2 methods. In the first method, the erythrocytes for grouping and cross-matching were suspended in a solution of 1% sodium citrate in physiologic saline to which had been added an equal volume of either 5% glucose in water or 1% glycine in physiologic

\* Gelatin solutions were supplied through the courtesy of Dr. D. Tourtellotte of the Chas. B. Knox Gelatine Co., Johnstown, N. Y.

saline. In the second method, which we have found to be easier and more satisfactory, the glucose or glycine solution was added to the serum-erythrocyte preparation as illustrated in Figure 1.

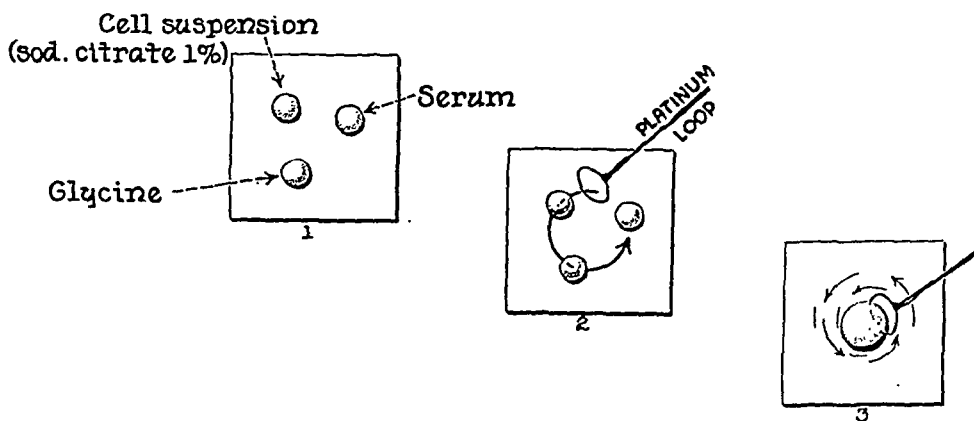


FIG. 1.—Method of cross-matching, using glycine.



FIG. 2.—Pseudoagglutination 30 minutes after mixture of cells and serum.



FIG. 3.—Pseudoagglutination 2 hours after mixture of cells and serum.

**In Vivo Observations.** In the cross-matching of blood of patients who had received gelatin infusions, hereafter called the recipients,

with the blood of normal individuals of the same blood group, hereafter called the donors, the resulting phenomena were uniform.

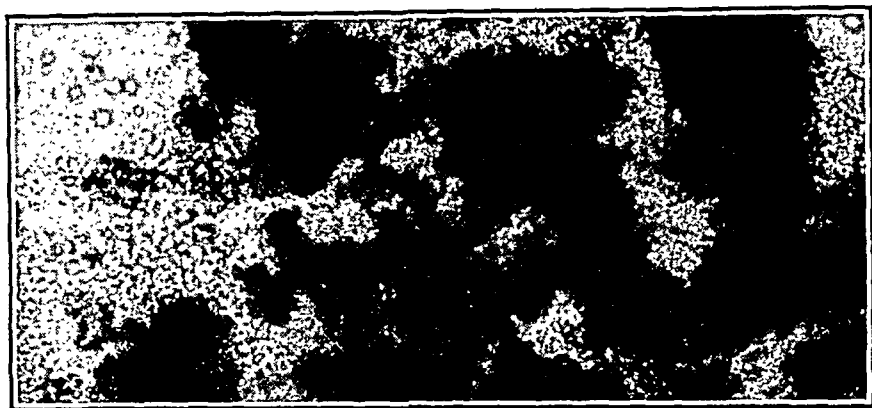


FIG. 4.—Actual agglutination with incompatible cells and serum.

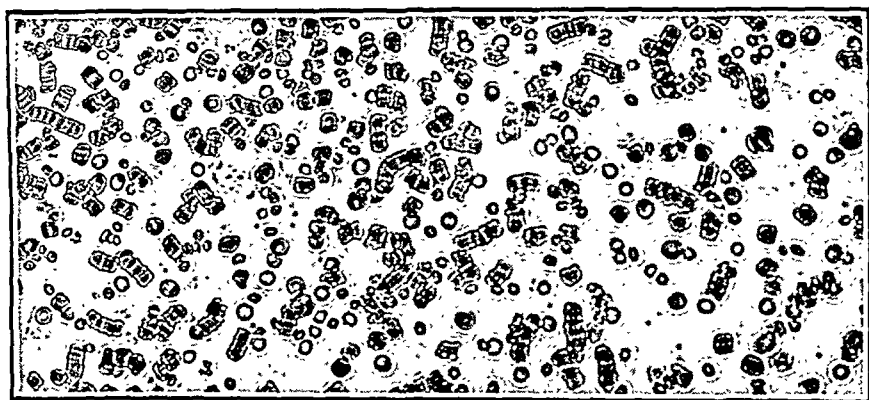


FIG. 5.—Effect of 5% glucose on pseudoagglutination seen in Figure 2.

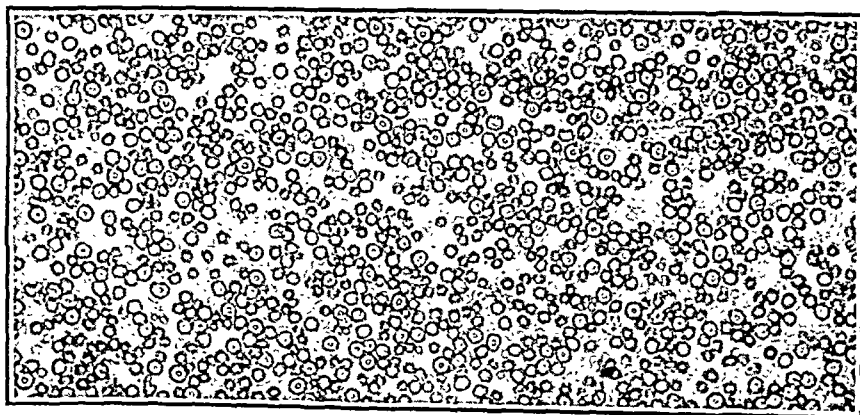


FIG. 6.—Effect of 1% glycine on pseudoagglutination seen in Figure 2.

There was never any abnormal appearance in the suspensions of recipients' cells in donors' sera. The phenomenon of pseudoagglutina-

tion was observed to some degree in all of the suspensions of donors' cells in recipients' sera.

Pseudoagglutination did not always show immediately after mixing recipients' sera and donors' cells. It was usually visible within 10 minutes and most marked in 30 minutes. There seemed to be no relation between the amount of gelatin infused or the time interval after infusion and the amount of pseudoagglutination. In some serum-erythrocyte suspensions there was so little pseudoagglutination that it could be considered a natural variation, and in most the picture was so definitely that of compact rouleaux that even the inexperienced observer would have had no difficulty in differentiating the appearance from that of actual agglutination.

In some of the serum-erythrocyte suspensions, however, there was sufficient pseudoagglutination to be confusing. Figure 2 shows the appearance of marked pseudoagglutination  $\frac{1}{2}$  hour after mixture of the cells and serum. Figure 3 represents the end-result after the abnormally long period of 2 hours. Both these photomicrographs were taken from the most marked example of pseudoagglutination we encountered. Figure 4 illustrates for comparison actual agglutination of incompatible blood as it is seen with this technique. Its strikingly different appearance is obvious even when compared with the 2-hour pseudoagglutinated specimen.

The addition of 5% glucose in water to the pseudoagglutinated specimens corrected in part the pseudoagglutination (Figure 5) while the addition of 1% glycine to the pseudoagglutinated specimen abolished it entirely (Figure 6).

In approximately 35 additional patients who had received previous infusions of gelatin varying from 500 to 3000 cc., no difficulty was encountered by the technicians of the blood bank of the Hospital of the University of Pennsylvania in subsequently typing or cross-matching their bloods.<sup>1</sup>

**Conclusions.** 1. Following the infusion of intravenous gelatin the erythrocytes exhibit pseudoagglutination, characterized by the formation of long and short, compact rouleaux. Even when these rouleaux are in close association their appearance is not that of clumping.

2. The phenomenon of pseudoagglutination in no way interferes with the grouping of blood in patients who had had previous infusions of gelatin.

3. In cross-matching the blood of patients who have received an infusion of gelatin, pseudoagglutination of varying degrees occurs in the normal donors' cells when mixed with such patients' sera. No such phenomenon is observed in suspensions of patients' cells in donors' sera.

4. Pseudoagglutination of erythrocytes is less marked when a 5% glucose solution in water is added to the erythrocyte-serum suspension.

5. Pseudoagglutination is abolished by the addition of a solution of 1% glycine in physiologic saline to the erythrocyte-serum suspension.

6. The use of a 1% glycine solution in physiologic saline in no way interferes with the grouping or cross-matching of blood.

7. In spite of the appearance of pseudoagglutination of erythrocytes in blood from patients who have received a previous infusion of gelatin, no practical difficulty has yet been encountered by our technicians in typing or cross-matching such blood.

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### DIGILANID AND THE THERAPY OF CONGESTIVE HEART DISEASE\*†

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IN the past few years two important developments have occurred in the field of digitalis, developments which promise to bring some interesting changes in digitalis therapy. The first of these developments was the adoption by the U.S.P. XII of the cat method as the official assay for digitalis. Thus, after many years of struggle, the cat method of assay was finally officially designated to replace the frog method of assay. The second of these developments, and probably the more important of the two, was the progress in the investigation of the pure glycosides‡ found in digitalis. These investigations seem to indicate that the pure glycosides may eventually replace the crude drug and thus eliminate the need for bio-assay.

While the cat method of assay is superior to the frog method and more closely approximates the values for man, it still has certain flaws which make it desirable to get away from a bio-assay method. Gold *et al.*<sup>4</sup> have shown in a series of studies that even digitalis glycosides with the same toxicity in cats show great differences in potency.

\* This study was aided by a grant from the Sandoz Chemical Works, Inc.

† Drs. Frederick Steigmann, Alfred Klein and Richard Martin who were collaborators in the early part of this work are now in the Service. Elizabeth M. Adles helped in the preparation of the statistical data.

‡ The term "glycoside" rather than glucoside is used in this paper according to the suggestion of Arthur C. DeGraff, *Bull. Acad. Med.*, **18**, 246, 1942.



While for a digitoxin type of digitalis the cat units may be taken as a fair guide to potency, great variations occur when using preparations closely related to digoxin or lanatoside C or any other cardio-active glycoside. Differences in absorption and elimination probably account for this fact. This inaccuracy in evaluation of potency becomes particularly important when one deals with digitalis extracts which vary in their glycosidal content according to crop, locality and year. Obviously the ideal solution of this problem will be the introduction of pure glycosides which can be adjusted by weight, thus affording accurate dosage.

With these facts in mind, we undertook to study clinically the therapeutic effect of a mixture of 3 pure crystalline glycosides of *Digitalis lanata* of known composition. This mixture (digilanid\*) was prepared by Stoll and his workers,<sup>6</sup> who found that the composition was constant and the preparation stable, and that when using it the dosage did not vary greatly in obtaining the therapeutic response in the same heart conditions. It was also his observation that, with a knowledge of its strength clinically, the tendency to produce toxic effects is lessened.

**Material and Method of Study.** Patients with congestive heart disease who entered the Cook County Hospital were used for this study. On entrance into the hospital, all cases of congestive heart failure were divided into two broad classes: (1) emergency, and (2) non-emergency.

In the emergency group, the cases of acute coronary occlusion were identified and eliminated from this study. The cases that were not emergencies were placed on bed rest and sedation for at least 3 days or longer, if the edema was subsiding as judged by the patient's loss of weight. Digilanid was, therefore, not started until it was determined whether the patient was unimproved or worse on bed rest alone.

The daily observations on all patients included:

1. Fluid intake.
2. Urinary output.
3. Weight.
4. Arterial pressure.
5. Heart rate and radial pulse.
6. Daily observations on state of congestive heart failure.

All cases had an electrocardiogram and 2 meter chest Roentgen rays taken on entrance and as frequently thereafter as indicated by their progress. Chest and abdominal aspirations were not done until after the patient had reached a stable weight level except in a few cases that became emergencies.

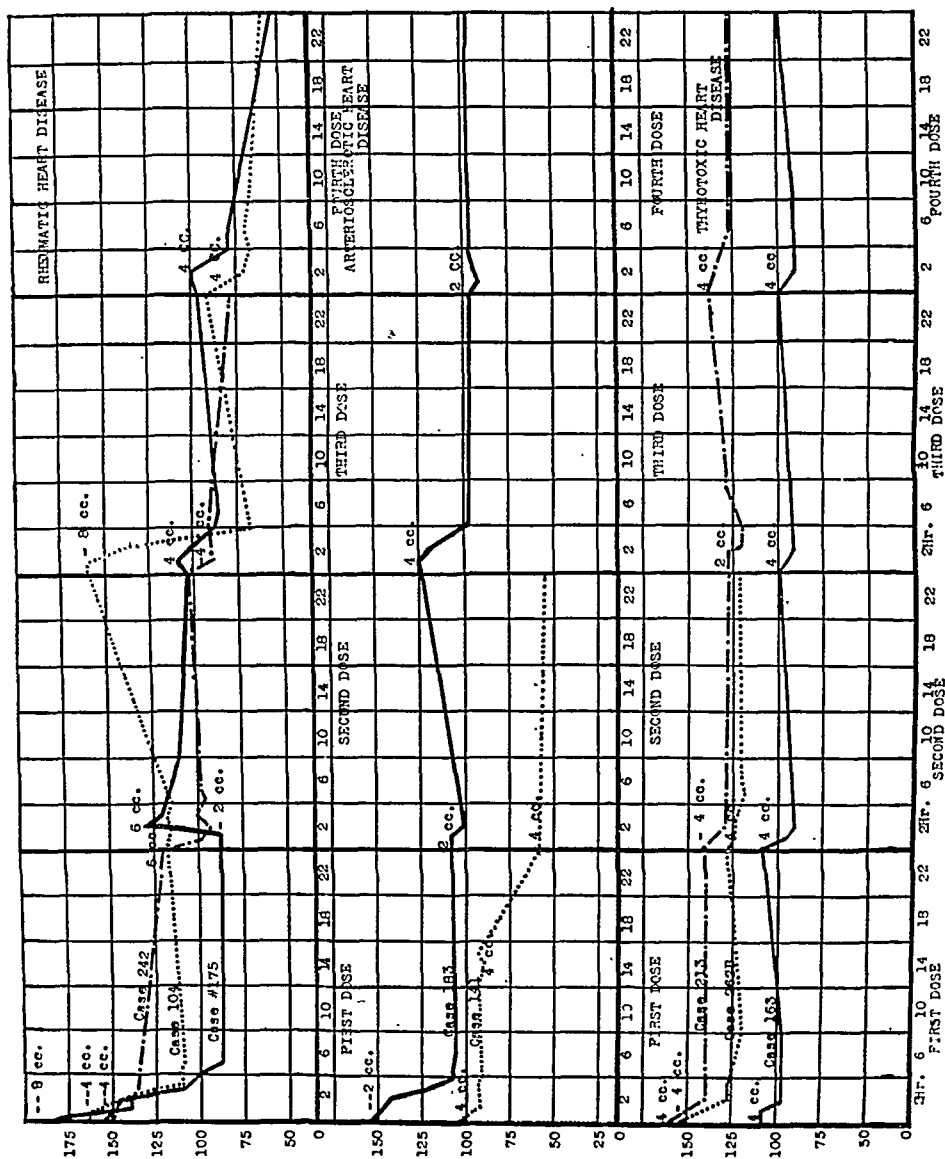
In those cases that still showed edema after weight had leveled off, other therapy was instituted.

Emergency cases were placed at absolute bed rest, given sedation (usually morphine) and 4 cc. of digilanid intravenously or intramuscularly when it was impossible to enter the veins because of the edema. Whenever possible, digilanid orally, 1 tablet 3 times daily, was started also. Additional intravenous digilanid was given only when indicated. It has never been necessary to give more than 2 intravenous injections of 4 cc. on the same day. This method of rapid digitalization was found to be more satisfactory than large doses by mouth, even in those cases that were not emergencies.

In most cases of the non-emergency group, the slow digitalization method was employed by giving 1 tablet of digilanid 3 times daily. These patients received no other therapy except sedation in the form of phenobarbital or

\* Digilanid supplied by Sandoz Chemical Works, Inc.

morphine as indicated. They were kept at absolute bed rest except for daily weighing until their weight reached a stable level. If all signs of congestive heart failure had subsided by then, the patient was allowed to get out of bed by easy stages.



GRAPH I

**Results.** *Intravenous Administration of Digilanid.* In 6 of the 9 cases, good clinical improvement occurred with slowing of heart rate; in 3 cases without much slowing of heart rate. Graph I shows the heart rate of 8 different patients on progressive digitalization with intravenous digilanid. The curves show essentially the action of the intravenous digilanid on the heart rate.

Case 175 illustrates a patient with fibrillation and with a very high heart rate who responded dramatically both objectively and subjec-



tively to the administration of 4 cc. of digilanid intravenously, showing a drop of 82 counts in the heart rate within 3 hours. (ECG's showed pulse rates of 190 and 108 respectively.)

One case which did not respond initially was a fibrillator with a heart rate of 104 before administration of digilanid. This case, a hypertensive, 44 years old, entered the hospital with high diastolic pressure and a complaint of severe dyspnea. Only after the second dose was a lessening of the dyspnea apparent.

From Graph I it may also be ascertained that in the larger proportion of cases the administration of 2 cc. did not produce as prompt or sustained an effect, leading to the conclusion that this is not the most effective dose. Likewise 8 cc. can be ascertained to produce a very great drop in heart rate, indicating that this dose is excessive.

While the accompanying tabulation (Table 1) shows only 2 instances in which 8 cc. was administered, these would indicate that the large drop in pulse rate resulting from the digitalis action lasted for a longer period of time.

TABLE 1b.—EFFECT OF INTRAVENOUS DIGILANID ON HEART RATE  
(IN 2 CC., 4 CC. AND 8 CC. DOSES)

Size of dose administered	No. of doses	Average decrease in heart rate (beats per min.)	Average time required for occurrence of major heart rate drop (hrs.)
2 cc. . . . .	10	10	1½
4 cc. . . . .	23	19	3
8 cc. . . . .	2	89	4½

A 4 cc. dose intravenously appeared to be the most effective dose, clinically and therapeutically.

*Length of Time Required to Secure Major Effect.* A dose of 2 cc. secured relatively little effect in 4 cases out of 5. A dose of 4 cc. secured a heart rate drop in all cases. In 9 instances out of 19 the major effect was accomplished in 2 hours or less; in 16 out of 19 instances the major effect was manifested in 4 hours or less. The intravenously administered digilanid, hence, requires about 3 hours to exert an effect on the pulse and other symptoms. With a dose of 4 cc. the digitalis action was apparent within 2 hours in 18 of the 19 administrations. In the 1 exception, the ultimate digitalis action was satisfactory, as far as ultimate pulse slowing was concerned. The length of time required to secure major heart rate drop is indicated in Table 1.

Graph I also shows that in most cases the dose of digilanid administered maintained the digilanid action throughout the 24 hour period.

*Oral Digilanid Administration.* Of the 18 patients who were given digilanid orally, all showed more or less clinical improvement within an average of 4 days. One showed improvement the 1st day after digilanid, 2 on the 2nd day, 6 on the 3rd day, 3 on the 4th day, 3 on the 5th day, 2 on the 6th and 1 on the 9th. This improvement was manifested by slowing of the pulse rate, disappearance of pulse deficit, increased urinary output, loss of weight, disappearance of edema, disappearance or decrease of orthopnea, disappearance of dyspnea.

TABLE 2.—RESULTS ON ORAL DIGILANID THERAPY (18 CASES)

Case No.	Age	Sex	Blood pressure		Pulse rate		Days on digilaid to begin-ning of pulse drop	No. days required to digitize patient	Tablets to digitalize (1 tablet: $\frac{1}{4}$ mg.)	Average digitalize per day to maintain dose	Main-te-nance dose	Days to edema lost		Pounds of edema lost	Total weight in hos-pital	Days lost	Clinical improvement				
			Initial	Final	Initial	At digit-alization															
												Syst.	Diast.					Api-cal	Per-iph.		
																				Syst.	Diast.
214	50	F	112	90	106	78	132	64	88	N.F.	1	9	34	3.5	1	15	16	22	30		
195	52	F	135	115	110	80	132	120	80	76	2	6	20	3.3	1	20	50	52	39	Orthopnea, 60° reduced, feels fine	
Rheumatic Heart Disease																					
181	63	F	170	110	135	86	120	106	84	N.F.	2	10	26	2.6	1	12	9	10	23	Orthopnea, dyspnea reduced	
206	68	F	150	90	164	80	124	N.F.*	96	N.F.	4	18	82	4.0	1	21	27	29	28	Orthopnea, 90° reduced to 5°	
214	56	M	164	98	134	86	92	N.F.	84	N.F.	6	13	39	3.0	?	13	20	20	19	Orthopnea, 90° reduced to 45°	
160	30	F	190	140	155	105	90	N.F.	80	N.F.	5	4	12	3.0	1	7	9	10	34	Orthopnea, dyspnea reduced	
220	40	F	190	124	190	98	100	N.F.	88	N.F.	9	15	21	1.4	1	21	19	20	27	Orthopnea, 60° reduced to 45°	
215	56	M	146	104	126	86	100	N.F.	84	N.F.	5	22	66	3.0	1	17	26	20	30	Orthopnea, 90° reduced to 60°	
223	63	F	136	90	120	76	138	N.F.	80	N.F.	4	20	59	3.0	2	12	14	30	29	Orthopnea, 60° reduced to 45°	
246	43	M	154	120	124	88	100	N.F.	60	N.F.	3	10	30	3.0	1	14	28	28	16	Orthopnea, 60° reduced to 30°	
209	55	F	160	90	160	100	96	N.F.	88	N.F.	3	7	21	3.0	1	14	22	22	16	Orthopnea, 30° reduced to 15°	
196	70	F	140	100	125	85	100	N.F.†	92	N.F.†	12	74	†	†	†	24	12	30	30	Orthopnea, 45° reduced to 0	
221	51	F	168	118	180	100	88	N.F.	76	N.F.	3	16	46	3.0	1	15	28	28	22	Orthopnea, 60° reduced to 15°	
228	29	F	190	138	180	100	120	N.F.	100	N.F.	6	18	50	2.9	1	22	11	14	51	Orthopnea, 60° reduced to 15°	
Hypertensive Arteriosclerotic Heart Disease																					
172	76	F	160	100	130	70	147	115	105	86	3	17	51	3.0	1	15	28	36	31	Orthopnea, 90° reduced to 0	
249	62	M	250	145	212	104	84	N.F.	74	N.F.	4	13	41	3.0	?	13	31	32	24	Orthopnea, 90° reduced to 45°	
224	26	F	110	70	110	70	84	N.F.	76	72	2	4	12	3.0	1	4	5	5	14	Orthopnea, 15° not improved	
Luetic Heart Disease																					
231	50	F	180	90	..	..	80	N.F.	82	N.F.	No drop	2§	§	§	§	17	19	23	22	Orthopnea, 60° reduced to 0	

\* N.F.: not fibrillating.  
† Final pulse rate, patient not digitalized on discharge from hospital.  
‡ Patient not digitalized, received 56 tablets in 14 days.  
§ Patient not digitalized, received 41 tablets in 13 days.

\* N.F.: not fibrillating.

† Final pulse rate, patient not digitalized on discharge from hospital.

‡ Patient not digitalized, received 56 tablets in 14 days.

§ Patient not digitalized, received 41 tablets in 13 days.

Drop in pulse rate became evident within 4 days as an average (in 1 case within 1 day, 3 cases on the 2nd day, 4 cases on the 3rd day, 3 cases on the 4th day, 2 cases on the 5th day, 2 cases on the 6th day, 1 case on the 9th day and 1 case on the 12th day). In 1 case with low initial rate, there was no drop in pulse rate on digilanid, but other evidences of clinical improvement occurred.

Digitalization as shown by slowing of the ventricular rate occurred, on an average, in 13 days, the shortest time being 4 days and the longest 22 days. In 2 days no digitalization occurred.

After reaching a basal weight on bed rest, these patients lost an average of 21 pounds within 15.5 days following digilanid therapy. The maximum weight lost was 50 pounds, the minimum 5 pounds. After the institution of digilanid therapy, 2 patients began to lose weight on the 1st day, 3 on the 2nd, 2 on the 3rd, 6 on the 4th, 2 on the 6th and 2 on the 10th.

Simultaneous with the weight loss there was a loss of edema, which paralleled the weight loss. Synchronous with the loss of weight and edema there was a marked improvement in the respiratory symptoms of these patients, the orthopnea and dyspnea decreased.

The output of urine increased after the first day in 7 cases, after the 3rd day in 3 cases, after the 4th day in 1 case, after the 7th day in 2 cases. There was no increase in the urinary output on digilanid therapy in 2 cases. One of these cases did not show a marked increase in urinary output on bed rest prior to institution of digilanid therapy.

Table 2 shows the number of days required to produce digitalization, loss of edema, the amount of digilanid necessary for digitalization and the amount required to maintain the patient after digitalization occurred.

On oral digilanid, the weight drop usually occurred before the pulse drop. In cases with regular rhythm, subjective improvement, plus weight drop and disappearance of edema, occurred even when there was no appreciable slowing of the pulse.

In the few hyperthyroid cases included in this study, the pulse drop was either insignificant or not as marked as in the other types of heart disease. However, the loss of edema and other signs of subjective improvement were as noticeable as in the others. The hyperthyroid group of heart disease required 2 or 3 times the amount of digilanid for a maintenance dose as did the non-hyperthyroid group. The findings would indicate that while digitalization alone is not sufficient for the treatment of thyrotoxic heart patients, it is a worthwhile adjunct in the therapy of these cases.

From the observation on this group of cases on oral digilanid, there seemed to be no relation between the dose of digilanid necessary for complete digitalization and the weight of the patient, the amount of edema, the presence of liver congestion or the age.

In only 4 of the 18 cases shown in the tabulation (Table 2) did symptoms of overdigitalization appear. In 2 of these instances there were no subjective findings, only signs of it in the ECG of 1 case and in the heart rate of the other. In 2 instances, nausea and vomiting

occurred; in 1 instance after 23 tablets in 17 days, in the other on the 59th day, 41 days after maintenance dose of 1 tablet t.i.d. had been established.

The oral use of these lanata glycosides seems to result in good therapeutic effect as noted from the pulse drop, loss of weight and edema, and disappearance of dyspnea and orthopnea. Furthermore, since comparatively smaller amounts of this drug can be given than of *Digitalis purpurea* preparations, there is less possibility of the occurrence of overdigitalization or other side effects.

TABLE 3.—RESULTS OF ATTEMPTED OVERDIGITALIZATION WITH DIGILANID  
(7 CASES)

Case No.	Dose to secure overdigitalization symptoms			No. days administered before overdigitalization occurred	Symptoms of overdigitalization (duration, days)				
	Total amount		Average per day (mg.)		Nausea	Vomiting	Bradycardia	Extrasystoles	Green vision
	Intravenous (mg.)	Oral (mg.)							
104	7½	2	2½	4	3	1	4		
141	2½	..	2½	1	..	..	6		
175	6	2½	8½	4	2	1	1		
236	1½	10½	1	12	..	..	2	12	
117	..	5½	0.9	6	..	..	..	3	
217	..	10	2½	4	2	1	..	2	
247	..	7½	1	8	..	..	..	..	1
Average for group:			2.7	5.5					

*Results of Attempted Overdigitalization With Digilanid.* An attempt was made to overdigitalize 7 cases by giving them large doses of both intravenous and oral digilanid. The average amount administered was 8 mg.; signs of overdigitalization appeared in an average of 5.5 days on the doses given (see Table 3). The lowest dose to produce overdigitalization was 0.9 mg. average daily dose. This brought on symptoms after 6 days. The highest dose was 2.7 mg. which produced signs of overdigitalization in 1 day. Bradycardia and extrasystoles were the first symptoms to appear and persisted longest, nausea and vomiting occurred in only 2 cases, vomiting persisted only 1 day.

**Summary.** Digilanid, a complex of lanatosides A, B and C, the pure glycosides of *Digitalis lanata*, adjusted by weight, was studied in 27 cases of congestive heart failure. Our investigation proves digilanid to be an effective cardio-active preparation, which has the advantages of purity, stability and accuracy as to dosage and therapeutic effect.

The average oral digitalizing dose is 12½ mg. (38 tablets) while the oral maintenance dose was found to be ½ mg. (1 tablet) in all but 1 case, which required ¾ mg. (2 tablets).

Digilanid intravenously in doses of 4 cc. (2½ mg.) proves to be a potent therapeutic agent in congestive heart diseases with either normal rhythm or auricular fibrillation. The intravenous administration in doses of 4 cc. is particularly indicated in cases of emergency, since its effect is reached within 3 hours, thus saving time of hospitalization.

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## AN EPIDEMIC OF PLEURODYNIA WITH PROMINENT NEUROLOGIC SYMPTOMS AND NO DEMONSTRABLE CAUSE

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SINCE epidemic pleurodynia was first described as a disease entity by Daac<sup>3</sup> in 1872, a number of outbreaks have been reported from Iceland,<sup>6</sup> the Scandinavian countries,<sup>7</sup> Germany,<sup>15</sup> England, and the United States.<sup>4</sup> It is said to be endemic on the island of Bornholm off the coast of Denmark, and in Europe is called Bornholm disease.

The unusual prominence of symptoms referable to the central nervous system constitutes the chief reason for adding to the literature this report of an outbreak of the disease among a group of student nurses. Ordinarily headache, photophobia, myalgia, and hyperesthesia are the only symptoms referable to the nervous system. Sylvest<sup>11</sup> mentions a case of encephalitis noted in one of the Swedish epidemics. Meningo-encephalitis does not, however, appear as a prominent feature of the disease prior to the epidemic reported from Weisen, Germany<sup>9</sup> in 1941. Cooper,<sup>2</sup> in describing coincidental outbreaks of lymphocytic choriomeningitis and epidemic pleurodynia in Cincinnati in 1935, speculated on the relationship of the 2 diseases. De Rudder,<sup>5</sup> in analyzing the epidemiologic data on anterior poliomyelitis and epidemic pleurodynia, was impressed by the similarity of the 2 diseases. He put forth the hypothesis that epidemic pleurodynia is a pathologic variant of poliomyelitis. Wohl<sup>14</sup> attempted bacteriologic confirmation of this hypothesis, but was unsuccessful. Williams<sup>13</sup> has recently reported the occurrence of myalgia most severe in the trapezius muscles but also involving the extremities in 5 English soldiers, appearing a few days after typhoid-paratyphoid immunization. Fever, headache, nuchal rigidity, Kernig's sign and an erythematous skin eruption were also noted. In 2 cases, the spinal fluid pressure was increased with an excess of lymphocytes present. One of these patients developed



pleuritic pain with a small homolateral pleural effusion during the course of the disease. Williams commented on the resemblance of the myalgia in his cases to that seen in epidemic pleurodynia. The most suggestive evidence that the etiologic agent of epidemic pleurodynia may be neurotropic, is found in the report by Howard *et al.*<sup>8</sup> of an epidemic occurring in Brooklyn in the summer of 1942. Among the 161 cases reported, there were 5 instances of meningitis and 3 of meningo-encephalitis. Many of their patients had headache, photophobia, and hyperesthesia of such severe nature as to suggest a central origin.

In its classic form, the onset of the disease is marked by sudden, sharp pain (accompanied by hyperesthesia), usually localized to the epigastrium and referred around the thorax to an area corresponding to the insertion of the diaphragm. This is soon followed by fever, which is accompanied by generalized headache, photophobia, myalgia, and occasionally by nausea and vomiting. The fever is peculiar in that it rises steadily to a peak (usually 102° to 103° F.) within the first 12 hours, and thereafter falls to normal during the next 12 hours. With the rising fever, there is an exacerbation of all symptoms; these subside as the fever falls. Such febrile and symptomatic exacerbations may recur several times before recovery, with intervening remissions of 1 to 2 days' duration, the course of the disease usually running from 5 to 10 days. Complications are rare, the commonest being pleuritis. Otitis media, sinusitis, orchitis, pyelitis, and very rarely, bronchopneumonia and fibrinous pericarditis are mentioned. The prognosis for recovery is excellent, no fatal cases having been reported. Except for some residual weakness, the symptoms usually disappear coincidentally with the subsidence of the last exacerbation. Occasionally cramplike pains in the legs and twinges of pleurodynia may recur for 3 or 4 weeks after defervescence. Since necropsy material has not been available, little is known of the pathology of the disease. Biopsy of the latissimus dorsi muscle in one instance<sup>12</sup> yielded no positive information. Unsuccessful attempts have been made to reproduce the disease experimentally by animal inoculation with pharyngeal washings from patients.<sup>2</sup>

The etiology of epidemic pleurodynia remains obscure. No attempts to isolate the causative organism appear to have been reported prior to 1924. In that year, Small<sup>10</sup> described a plasmodium in the erythrocytes of 2 patients with the disease, but the etiologic importance of this organism was not established. In 1935, unsuccessful attempts were made to recover an organism or virus from blood, spinal fluid, and nasal washing from patients in the Cincinnati epidemic.<sup>2</sup> Unsuccessful attempts were likewise made to identify the causative agent in the cases described in this report (*vide infra*).

The group of 16 cases, here reported, occurred among the student nurses in the Training School of the Hospital of the University of Pennsylvania. The first case appeared August 7, 1943, in a nurse just returned from an affiliate service at the city's communicable disease hospital. No case of the disease was known to have occurred at this

institution either prior or subsequent to its appearance in this patient. Other cases of pleurodynia were observed among the city's general population at this time, so that it might have been introduced into the nursing school by a case outside the institution. Fresh cases continued to appear among the personnel of the Training School at 8 to 14 day intervals for 3 months until November 11, 1943, when the last case was seen. The dates of appearance were: August 7, 22, 31; September 1, 2, 3, 12, 15, 21, 23, 28; October 2, 4, 27; November 11.

The first 2 cases were classical in their symptomatology and course. The onset in each case was marked by nausea and vomiting without prodromal symptoms. Headache, fever, photophobia, and pleurodynia appeared almost immediately. The symptoms subsided coincidentally with the fever only to be followed by several exacerbations at 24 to 36 hour intervals. The disease lasted 10 and 12 days in these 2 patients. It was with the appearance of the 3rd case that affection of the central nervous system by the etiologic agent was first noted. The 3 cases presenting the most striking evidence of involvement of the nervous system are summarized below:

**Case Reports.** CASE 1. M. C., a 19 year old student nurse, attended the first 2 cases of pleurodynia. Six days after her first known exposure, she complained of an intense, generalized headache. This was her only symptom, and fever of  $100.8^{\circ}$  F. was her only physical finding on admission. By the following morning she had developed slight nuchal rigidity, a positive Kernig's sign, and photophobia of such severity that not only the shade but the black-out curtain in her room had to be kept drawn to give her relief. A lumbar puncture was done, and perfectly clear fluid under a pressure of 155 mm. of water was obtained. On microscopic examination, the fluid contained 20 cells per 100 cc., all lymphocytes. The protein content was 60 mg. per 100 cc., the sugar 51 mg. per 100 cc. Her initial total leukocyte count was 8700 and never exceeded this level. The differential spread was normal. Both blood and spinal fluid cultures were negative.

The patient's temperature dropped to normal on the 3rd hospital day and rose only once thereafter, reaching  $99.4^{\circ}$  F. on this occasion. The headache, nuchal rigidity, and photophobia disappeared 3 days later, and she was discharged 10 days after admission. Ten days later, she was readmitted with typical diaphragmatic pain, which was made worse by deep inspiration, headache, nausea, vomiting and fever. The course of the disease was somewhat atypical in that there occurred each evening a rise in temperature to  $99.2$ – $4^{\circ}$  F., accompanied by disproportionately severe generalized headache and myalgia. The low grade daily fever with similar symptoms persisting over 2 to 3 weeks was seen in 5 other cases.

CASE 2. Even more striking involvement of the central nervous system is illustrated by the case of Miss D. G., a 21 year old nurse who gave a history of sudden onset of nausea, vomiting, diarrhea, severe headache, and lumbar pain. The headache was the most persistent symptom, and was only temporarily relieved by morphine. The day following admission, she suddenly developed severe bilateral sciatic pain and hyperesthesia manifested by diminished response to pin-prick over the area supplied by the first lumbar and the first and second sacral roots. She preferred to lie flat on her back with her legs flexed on a pillow at an angle of 45 degrees. Straightening the legs or flexing them any more acutely caused severe pain in the lumbar region. In addition to the pain and hyperesthesia, there was marked tenderness to palpation of the muscles of the legs and lower lumbar erector spinæ group. All tendon reflexes remained normal, and no pathologic reflexes could be elicited. Her optic disk margins were hazy, but there was no measurable

papilledema and the fundi were otherwise normal. The spinal fluid was clear, and under a pressure of 150 mm. of water, no cells were found; the protein content was 25 mg. per 100 cc. Except for aortic and mitral murmurs, which had been present prior to this illness, and the hyperesthesia mentioned, the physical examination was negative. The temperature did not rise above 99.4° F. at any time, and only reached this level the first 3 days of her illness. Her symptoms disappeared as dramatically as they had occurred on her 8th hospital day. She was discharged on her 10th day and has remained well since. Pleurodynia was not present at any time, but in view of the patient's close association with typical cases of epidemic pleurodynia, it seemed probable she suffered from an atypical form of the disease. The neurologic consultant who saw this patient as well as several others included in this report, made the following comment: ". . . if the sensory changes are authentic, they suggest involvement of the spino-thalamic tract of the spinal cord, in addition to meningeal signs. Whenever this agent appears, it seems to have some propensity for invading the nervous system."

CASE 3. At the peak of the epidemic, 1 case occurred with a clinical picture suggestive of encephalitis. The patient was a 20 year old nurse, who had also been in attendance on her ill classmates. After 4 days of severe headache, she became stuporous and remained in this condition for 3 days. During this time she could be roused, and although her mental processes were sluggish. She was well oriented and could answer questions coherently. When not disturbed, she lapsed back into stupor. As she gradually became more wakeful, episodes of unconsciousness were noted. These were characterized by a fall in respiratory rate to a level of 3 to 6 per minute and by loss of consciousness. She could not be roused during these attacks by painful stimuli, but the administration of oxygen appeared to terminate them. At no time did she become cyanotic, although one episode is said to have lasted an hour. The patient was not aware of these attacks and exhibited no aural symptoms. The periods of unconsciousness occurred 2 to 3 times daily for a week, and thereafter decreased in frequency and finally disappeared altogether at the end of 3 months.

Physical examination was negative except for some lumbar tenderness and haziness of the optic disks similar to that seen in several cases of pleurodynia.

Determinations of blood sugar and urea nitrogen, serum calcium and inorganic phosphorus, plasma proteins, chlorides, and carbon dioxide combining power all yielded normal values. Examination of the spinal fluid likewise showed nothing abnormal. Roentgen ray of the skull were negative. An electro-encephalogram made following her initial stupor showed no abnormality. A tracing made during a subsequent period of unconsciousness showed neither an abnormal nor normal sleep rhythm, which suggested that conversion hysteria might be responsible for her lapses into unconsciousness. No further evidence has, however, been obtained to support this diagnosis.

During the 2 months which followed her acute episode, she had 5 similar attacks. She has since remained well.

**Comment.** Even in the cases which exhibited the typical chest pain and gastro-intestinal symptoms of pleurodynia, irritation of the nervous system was the most striking feature. Because of persistent, boring headache, most of the patients preferred to lie perfectly flat and completely still. Any motion of the head or trunk was said to make the pain unbearable. Morphine, in doses of  $\frac{1}{6}$  to  $\frac{1}{4}$  grain, gave only transient relief. In only 1 or 2 instances was there relief following the removal of spinal fluid, so that irritation rather than pressure appeared to have been the cause of the headache. Several patients complained of unusual sensitivity to noise and mechanical vibrations, suggesting the possibility of hypothalamic involvement. Haziness of

the optic disk was a common finding during the course of the disease, with a return to normal a week or two after recovery.

TABLE 1.—CLINICAL DATA PERTAINING TO PATIENTS WITH PLEURODYNIA

Patient	Age	Prodromal symptoms	Initial symptoms	Location of pain	Hyperesthesia
1. E. L.	21	None	Headache; pleurodynia	Head; along attachment of diaphragm	In area of pleurodynia
2. L. B.	21	Chill; pharyngitis	Vomiting; pleurodynia; generalized myalgia	Head, back and along diaphragm	About thorax; over flexors of legs
3. M. C.	19	None	Headache; malaise; fever	Head, back, over flexors of legs	In areas of pain
4. M. A. B.	19	Exanthem on arms and trunk 3 days prior to onset	Pleurodynia; headache	Head, back	Generalized
5. R. R.	20	None	Nausea; vomiting; malaise; headache	Along diaphragm, lumbar, sciatic distribution	Corresponding to pleurodynia
6. D. G.	19	None	Nausea; vomiting; diarrhea	Lumbar region; sciatic distribution	Flexors of legs
7. E. T.	19	None	Pleurodynia; headache; malaise	Corresponding to diaphragmatic attachment	In area of pain
8. B. M.	19	Headache for 1 wk.	Stupor	Lumbar area	Corresponding to area of pain
9. M. C.	19	Headache; malaise	Pleurodynia; headache; nausea; vomiting	Generalized abdominal, along diaphragm	Generalized
10. M. A.	19	Cough; pharyngitis	Sore throat; pleurodynia	Along diaphragmatic attachment	In area of pain
11. C. Q.	20	Cough; pharyngitis	Headache; pleurodynia	Along diaphragmatic attachment	In area of pain
12. M. T.	20	Pharyngitis	Pleurodynia; malaise	Prostrating myalgia	Generalized
13. M. E.	18	Rhinitis; sore throat	Pleurodynia; malaise	Along diaphragmatic attachment	Generalized; objected to weight of bedclothes in areas of pain
14. D. S.	20	Malaise for 5 days	Chill, fever, sore throat; nausea; vomiting	Epigastric, over flexors of leg, pleuritic	In areas of pain
15. A. L.	19	None	Headache; pleurodynia	Along diaphragmatic attachment	Transiently in area of pain
16. H. E. B.	19	Malaise for 3 days	Headache; pleurodynia	"Breakbone" type of malaise	Generalized (also objected to weight of covers)

Clinical data pertaining to all the patients studied in the outbreak are shown in Table 1 and Table 2.

The significant features of Tables 1 and 2 may be summarized briefly as follows: Pleurodynia was the commonest initial symptom, occurring in 10 patients.

Mild prodromal symptoms referable to the upper respiratory tract

were noted in 5 patients. One patient presented a mild erythematous skin eruption on the forearms and abdomen 3 days prior to onset.

All patients complained of severe headache and only 4 failed to show epigastric or thoracic pain.

TABLE 2.—FURTHER DATA ON CASES OF PLEURODYNIA

Patient	Meningeal signs and symptoms	Duration of disease (days)	No. of exacerbations	Sequelæ	Significant laboratory data
1. E. L.	Headache	11	3	Headache; pleuritis	Leukopenia; W.B.C. 5000 and below
2. L. B.	Headache; photophobia	16	5	Cramping pains in legs	W.B.C. 7200 to 5000
3. M. C.	Stiff neck; Kernig's sign	10	Daily	None	Spinal fluid findings: 20 cells (lymphocytes), 155 cm. H <sub>2</sub> O pressure, culture neg., leukopenia, W.B.C. 4000
4. M. A. B.	Marked hyperesthesia	6	1	None	Initial W.B.C. 10,000; dropped to 5000 2nd day
5. R. R.	Bilateral patellar clonus	22	Daily low grade fever	Cramping pains in legs	Spinal fluid findings: 76 cells (lymphocytes), 150 cm. H <sub>2</sub> O pressure, 24.4 mg. protein, culture neg., W.B.C. averaged 8200
6. D. G.	Diminished pain preception over L <sub>1</sub> , S <sub>1</sub> and S <sub>2</sub>	9	1	None	Spinal fluid findings: 150 cm. H <sub>2</sub> O pressure, no cells, culture neg., 30 mg. protein, W.B.C. 8500
7. E. T.	None	7	None	Pains in legs	None
8. B. M.	Encephalitis	22	5	Loss of consciousness on 6 different occasions in 2 months following discharge	Spinal fluid findings: 230 cm. H <sub>2</sub> O pressure, no cells, culture negative, 45 mg. protein, W.B.C. dropped from 12,000 to 4000 in 3 days
9. M. C.	Headache; photophobia	10	None	Headache; sl. myalgia	W.B.C. 9000
10. M. A.	None	7	5	None	W.B.C. 9600
11. C. Q.	Headache; photophobia	30	Daily rise to 99.4° F.	Headache and pain in legs for 1 month	W.B.C. 7000 to 5200
12. M. T.	Intense photophobia; headache; hyperesthesia	60	10	Headache; myalgia recurs with every cold	Leukopenia, W.B.C. 5800, 4700 5600
13. M. E.	Headache; photophobia	14	2	None	W.B.C. 7800
14. D. S.	None	7	None	None	W.B.C. 8500
15. A. L.	Headache	15	Daily rise to 99.2° F.	Pleuritic pain and myalgia	W.B.C. 6500
16. H. E. B.	Intense photophobia and headache for 1 week	23	3	None	Spinal fluid findings: 145 cm. H <sub>2</sub> O pressure, cells 1 (lymph), 28 mg. protein, culture neg., W.B.C. 5800, neutrophils 60%, lymphocytes 18%, monocytes 2%

Hyperesthesia usually referred to the thorax or legs was seen in 13 cases.

Other evidence of meningeal irritation (photophobia and/or nuchal rigidity) was present in 12 patients.

Kernig's sign was found in 1 patient.

The duration of the disease varied from 7 to 16 days (average about 14).

The number of exacerbations varied from 1 to 10, the usual number being 3.

Nine patients presented sequelæ which included headache, pleuritis, generalized weakness, and myalgia.

The only consistently significant laboratory finding was leukopenia, which was present in 9 cases, and usually developed on the 2nd or 3rd day. The depression in the total leukocyte count usually lasted about 2 weeks. The low total leukocyte count usually lasted about 2 weeks. The total count varied from 3000 to 5000, with a uniform reduction in the differential formula. Leukocytosis was not observed in any case. Blood and spinal fluid cultures were negative.

The literature contains no reference to therapeutic agents or procedures of specific value in epidemic pleurodynia, and for the present only symptomatic and supportive therapy seems possible. The treatment employed in the cases reported here consisted of salicylates, barbiturates, opiates, parenteral fluids, vitamins, and various supportive measures such as strapping the chest, ice caps, and so on. None of these agents was of much benefit. In 2 cases relapse occurred 4 and 5 times and prostration was so severe that pooled adult plasma was given with apparent benefit.

Drs. G. and W. Henle, of the Children's Hospital of Philadelphia, kindly attempted to isolate the causative agent from material obtained from our patients. Blood, spinal fluid, nasal washings, and urine were injected into hamsters, mice, guinea pigs, rabbits and chick embryos. This material was obtained from our patients at various times during their illness; in 2 cases on the day of onset, in 2 on the 2nd day, in 4 on the 10th day, and, in 1, 15 days after recovery. All the animals remained well. Complement-fixation tests, employing antigenic material derived from the influenza virus and that of lymphocytic choriomeningitis, were performed on 8 of our patients with entirely negative results.

**Summary.** An outbreak of epidemic pleurodynia, affecting 16 young women in a nurses' training school, is described. The source of the epidemic was not determined. Signs and symptoms referable to the central nervous system were unusually prominent. Such neurologic manifestations dominated the clinical picture of 11 patients. In 3 of these patients the symptoms resembled those of meningo-encephalitis, suggesting that the etiologic agent might be neurotropic. Attempts to reproduce the disease in animals were unsuccessful.

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## THE RELATIONSHIP OF COLD AGGLUTININS TO THE COURSE OF PRIMARY ATYPICAL PNEUMONIA

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SEVERAL investigators have recently discovered that cold (low temperature) agglutinins of varying titer are found in the sera of some patients suffering with primary atypical pneumonia.<sup>5,7</sup> Others have observed complications, such as peripheral vascular thrombosis<sup>2,4</sup> and acute hemolytic reactions,<sup>1</sup> following an attack of this pneumonia. High titers of autohemagglutinins (cold) were implicated in all of these unusual reactions and seemed to be directly responsible.

During the fall months of 1943, a small epidemic of primary atypical pneumonia occurred here and was followed closely in the laboratory, particularly in regard to the changing titer of serum cold agglutinins. One death is reported in this series with interesting pulmonary pathology. Although all of the characteristic cases of atypical pneumonia in this group were found to have high titers of cold agglutinins, a subsequent epidemic showed that this reaction was not consistent. None of the patients with the disease during the winter months developed autohemagglutinins but many were found to have strongly positive Kahn precipitin tests. A later report will deal with this phenomenon.

**Criteria for Diagnosis.** The symptoms, physical signs and clinical course of the patients with primary atypical pneumonia in this group were identical to those described by Reimann *et al.*<sup>8</sup> and Dingle *et al.*<sup>3</sup> The diagnosis was made after the patient had satisfied the following tests:

1. Symptoms of sore throat, headache, chills and fever, paroxysmal dry cough, substernal pain, generalized aches.
2. Negative lung signs from 4 to 7 days, changing to râles, without consolidation usually in the lower lobes.
3. Chest Roentgen ray\* evidence from the 4th to 10th day.
4. Negative sputum examination for pathogenic bacteria.
5. Normal W.B.C. count and differential, or slight leukocytosis.<sup>11</sup>

In this way, 15 patients were found to comply to this critical standard.

**Methods.** A regimen was worked out so that each patient suspected of developing primary atypical pneumonia had blood withdrawn for cold agglutinin titration every 4th day after the 1st or 2nd hospital day. The day of the disease indicated on the figures was reckoned from the onset of the symptoms.

Cold agglutinin determinations were performed by using serial dilutions of fresh serum (not inactivated)† and adding washed 2% suspension of Group O cells. Fresh suspensions of washed Group O cells were checked against a negative and known positive serum. Readings were made under magnification immediately after removal from overnight icebox incubation. The racks were then allowed to stand at room temperature or warmed in the incubator to insure resolution of the R.B.C.. Invariably, the cells became smooth upon warming to 37° C.

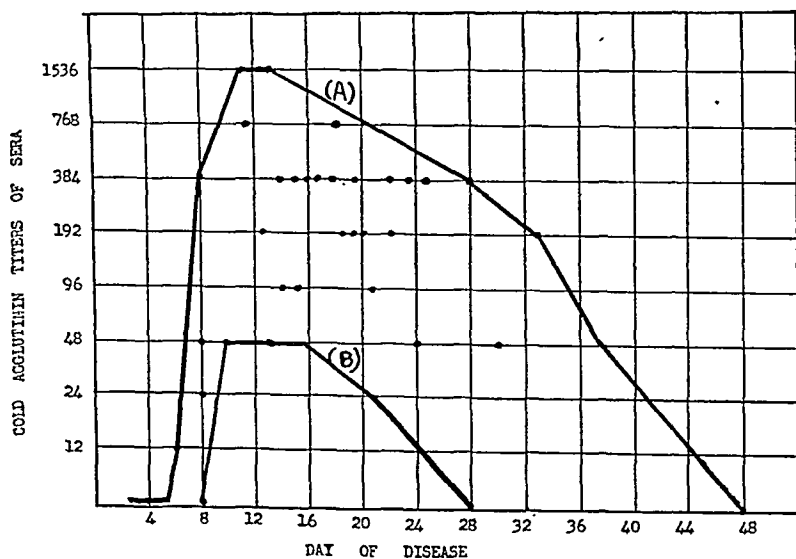


FIG. 1.—Cold agglutinin titer determinations of 15 patients with primary atypical pneumonia; taken during the course of disease.

**Results.** Figure 1 shows a spot graph of 49 cold agglutinin determinations during the illness of 15 patients with primary atypical pneumonia. The solid top line (A) represents the earliest positive test, the highest titer and longest duration of cold agglutinins encountered in these patients. The lower line (B) represents latest appear-

\* I wish to thank Major George H. Brown, Chief of X-ray Service, who read all of the chest films.

† Several positive sera were inactivated and found to give the identical titer of the original serum.



ance, the least titer and the earliest disappearance of cold agglutinins. Highest titers were encountered from 11th to 13th day of illness.

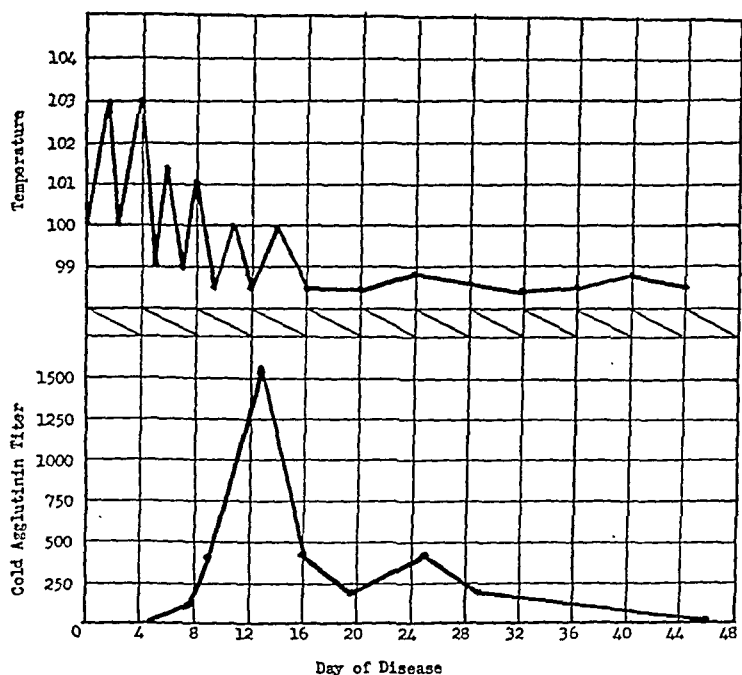


FIG. 2.—Cold agglutinin titer change in the course of illness of the usual patient in this group with primary atypical pneumonia.

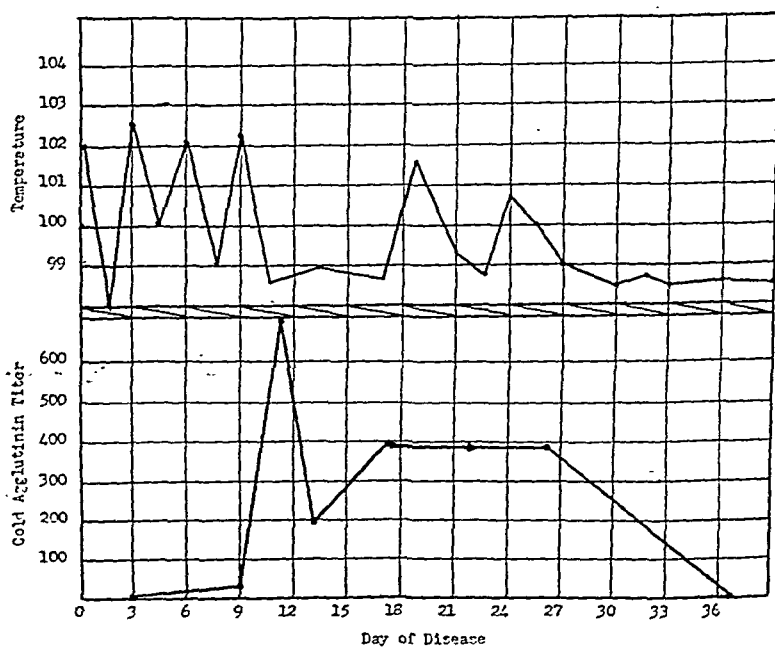


FIG. 3.—Cold agglutinin titer change in one patient with a relapse of fever and symptoms.

Figure 2 illustrates the titer of the cold agglutinin synchronized with the temperature record during the course of a typical case of "virus" pneumonia. The peak of the serum titer is reached on the 13th day as the temperature is on the decline and then its agglutinability decreases sharply, lingers at a lower titer, finally going to zero after a few days of normal temperature. From personal observation, these patients are most uncomfortable at the peak of the cold agglutinins when the paroxysms of cough are difficult to control even with codeinè.

Figure 3 is a record of cold agglutinins and temperature and is similar to Figure 2 up to the 15th day when a relapse occurred with increased temperature and spreading lung signs. This is reflected also in the cold agglutinin titer which increased and held a plateau until the temperature finally receded.

**Complications.** Two patients in the group became seriously ill on the 10th day of their illness, corresponding to the peak of the cold agglutinin titer. Instead of improving steadily with fever by lysis, these patients had emesis of food and water, increasing dyspnea and a remarkable spread of pulmonary signs so that moist râles were clearly audible in all lung fields. This was accompanied by fever rise and leukocytosis.

**Case Reports.** **CASE 1.** A soldier was admitted to the Station Hospital on Aug. 16, 1943, complaining of sore throat, cough, fever and headache for 2 days prior to admission. Physical examination revealed only a distinct pharyngitis and W.B.C. equaled 12,000, with differential of 74 neutrophils and 26 lymphocytes. He was started on sulfathiazole but at the end of 3 days, the drug was stopped because the temperature continued to rise to 102 to 103° F. daily, and he had moderate nausea and emesis. However, no physical signs gave a hint as to the cause of the fever and the W.B.C. remained at 11,400 (79% neutrophils, 19 lymphocytes, 1 monocyte and 1 eosinophil). A study of blood smears was negative for malaria and a corrected sedimentation rate was 41. On the 9th day of illness, a Kahn test was reported positive. The patient complained of numbness of his fingers, although examination of the extremities was negative.

On the 10th day, his condition became rapidly worse, with nausea, emesis, dehydration, dyspnea and for the first time moist râles were heard at the left lower lobe. His temperature rose all day and the râles spread rapidly throughout the entire left lung and right middle and lower lobes. Sputum for pneumococcus typing revealed very few organisms and no typing could be obtained. The W.B.C. was now 24,000 (76% neutrophils, 23 lymphocytes and 1 eosinophil). He was placed in an oxygen tent. Fluids and intravenous sulfonamide were given. Catheterization was necessary for the next 3 days as he gradually improved, although his respirations were of Cheyne-Stokes type for 24 hours. A portable chest Roentgen ray was unsatisfactory. During the next 15 days, the patient gradually improved with clearing of the chest findings, a drop in the sedimentation rate, a negative Kahn precipitin test and normal blood counts. In this phase of recovery, a cold agglutinin test was found to be markedly positive both to his own cells and O cells. No signs of a hemolysin were observed.

**CASE 2.** A soldier was admitted to the Station Hospital complaining of a sore throat, cough with chills and fever although physical examination was negative. Sputum for pneumococcus typing was negative on the 5th day when râles were heard in the lower lobe bilaterally. Sulfathiazole therapy did not alter his course of daily fever rise and continued cough. On the 10th day,

he became moderately dyspneic after 12 hours of nausea and emesis of food and water. Parenteral fluids were given and oxygen tent atmosphere instituted after stopping sulfathiazole therapy. Within a few hours, the entire lung fields were filled with râles and he expectorated blood-streaked frothy sputum. Despite supportive measures, pulmonary edema increased and he expired 16 hours after the onset of dyspnea. A cold agglutinin titer taken 24 hours before death was positive 1:192.

An autopsy was done immediately. During the dissection, it was noted that no fluid blood escaped and that the vessels and heart contained clotted blood. The lungs presented the important findings. They were heavy, voluminous, and deep purple-red hemorrhagic areas shown through the pleura. On section, fluid exuded freely from the surface which was mottled with distinct hemorrhagic areas the size of a pea and larger areas involving one-third of the lobe. The pulmonary vessels contained blood clots but no organized thrombi were discovered despite the gross pathologic picture, resembling multiple hemorrhagic infarction. Culture from the trachea resulted in the growth of a Group G hemolytic streptococcus which was neither fibrinolytic nor pathogenic for mice. Cut lung sections were sterile.

Microscopically, the bronchi contained neutrophil cells and the mucosa was hyperemic while the alveoli were engorged with red blood cells, large mononuclear cells and fluid. This engorgement was more acute in perivascular areas. All other organs were normal.

**Discussion.** Autohemagglutinin in significant titers seem to follow the course of primary atypical pneumonia, rising as the fever abates, reaching a peak as chest signs and symptoms are most acute, and receding as the lung clears and temperature returns to normal. This is the usual course of events. However, 1 patient had a relapse of fever and symptoms, whereupon the "cold" agglutinins rose again (Fig. 3), then decreased with recovery.

TABLE 1.—COMPARISON OF AGGLUTINATION OF O CELLS BY POSITIVE SERUM AND PRECIPITATED GLOBULIN FRACTION

	Patient H		
	Serum	Globulin	Control globulin
1:12 . . . . .	+++	++	—
1:24 . . . . .	+++	++	—
1:48 . . . . .	++	+	—
1:96 . . . . .	+	+	—
1:192 . . . . .	+	+	—
1:384 . . . . .	±	+	—
1:768 . . . . .	—	—	—
1:1536 . . . . .	—	—	—
C . . . . .	—	—	—

Since the cold agglutinin appears 8 to 12 days after the onset of the disease and disappears upon recovery, it suggests an antigen-antibody reaction. It is conceivable that the virus acts as an antigen within the reticulo-endothelial cells, and after an incubation period liberates the globulin fraction which produces the cold agglutinin effect. Most antibodies are found in the globulin portion of the serum protein, therefore it seemed probable that this agglutinin would be found there. Positive high-titered cold agglutinin serum was precipitated by 43% saturation of ammonium sulfate, dissolved in saline, reprecipitated, redissolved in saline and then dialyzed repeatedly against cold saline.

A negative serum was treated the same. The final volume of dialyzed protein was determined to estimate the dilution. Then these solutions were set up in serial dilutions with washed O cells. The rack was allowed to stand overnight in the icebox. Table 1 shows the results.

The globulin fraction was not quite as strong in the low dilution but is of equal titer. This experiment was repeated with other serum and found correct. Therefore, it seems that cold agglutinins are for the most part in the globulin protein fraction.

A most interesting question arises: Of what clinical significance is the high titer of cold agglutinins occurring simultaneously with acute pulmonary edema and death in one instance? This seems to be more than a coincidence, since it occurred twice while each patient was in his 10th day of illness when cold agglutinins were high. The pathological picture seen in the fatal case was strikingly similar to multiple pulmonary infarction with edema but without thrombosis. It seems logical, however, that small groups of agglutinated cells could form in a relatively cold extremity,<sup>10</sup> act as multiple emboli, and cause the pulmonary "infarction" picture. Death may be so rapid that organization of these emboli would not take place. *In vitro*, the separation of warmed cold agglutinated cells takes several moments. Larger masses of these red blood cells may remain compact upon reaching the lung.

Although few studies have been made on the occurrence of the titered cold agglutinins in various diseases, those which are reported indicate low specificity. Stats<sup>10</sup> mentions Raynaud's syndrome, acute and chronic hemolytic anemias, trypanosomiasis, acute bacterial infections, liver cirrhosis, leukemia, pernicious anemia, lymphoblastomas and bland venous thrombosis, as diseases producing cold agglutinins. In order to determine the usefulness of the test in excluding other diseases, a study of sera from lobar pneumonias and bronchopneumonias were compared in titer to primary atypical pneumonia.

TABLE 2.—COMPARISON OF SERA FOR COLD AGGLUTININS IN THREE TYPES OF PNEUMONIA

Disease	No. cases	No. cold agglutinins performed	Negative tests on these days	Positive tests on these days	Titers
<i>Pneumonia:</i>					
Primary atypical . . .	15	49	3, 4, 6, 8, 28, 48	6, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 26, 30, 36	Av. above 1:96
Lobar, acute (types known)* . . . .		7	8, 7, 6(2), 5, 4, 3	0	0
Broncho (no specific bacterial types) (a)	12	24	2, 3, 4, 5, 6, 7, 9(2), 10, 11, 12, 14(3), 16	0	0
(b)	6	9	....	4, 5, 6, 7, 8(3), 10, 13	Av. below 1:48
<i>Infectious mononucleosis</i>	5	5	(a) 4 serums negative (b) Heterophil titers from 112-7168	....	1 positive 1:48

\* These patients responded rapidly to sulfonamide therapy and diagnosis was not questioned. In 6 to 8 days they were feeling well with pneumonia resolving completely.

Bronchopneumonia was separated from either primary atypical or lobar pneumonia because it did not conform strictly to either. This disease ran a short course of fever, early, brief, pulmonic signs, negative sputum typing, irregular response to sulfonamides, and occasionally low-titered cold agglutinins. Perhaps these cases represent a mild form of primary atypical pneumonia. Usually the bacterial flora of the sputum was non-hemolytic or viridans streptococci. One serum of five in infectious mononucleosis cases gave a low titer of cold agglutinins. One patient with lymphocytic choriomeningitis gave a serum cold agglutinin titer 1:96 on the 8th day. Serums showing a cold agglutinin titer of 1:48 or above between the 8th to 16th day of an acute pulmonary disease would seem to indicate primary atypical pneumonia.

Landsteiner and Levine,<sup>6</sup> in reference to autoagglutinins, state that "The stronger sera were found to be active when kept in the icebox for months. Weak sera deteriorate in a few days." Fifty-one positive cold agglutinin blood sera were saved without preservative in the icebox to observe the effect of time upon the titer. It was found that the sera maintained their titer for 6 weeks but, upon the 12 week test, all sera had decreased in titer and some dropped to zero. A slight growth appeared in some, but even the clear uncontaminated sera decreased about the same amount.

**Summary.** Cold agglutinin titers were followed in 15 cases of primary atypical pneumonia. The reaction was negative for 6 days, became positive in 6 to 8 days, reached a peak between the 10th to 14th day, then gradually decreased during convalescence.

High titers of cold agglutinins were observed during the most serious stage of the disease (10 to 14 days). One patient became critically ill and another died in this stage; both had pulmonary edema.

A possible explanation is offered for the coincidence of high agglutinin titer and marked pulmonary edema with hemorrhagic "infarction."

Not all epidemics of primary atypical pneumonia are found to produce serum cold agglutinins. However, repeated cold agglutinin titers are of value in following the course of an acute pulmonary infection to aid in diagnosis and anticipate complications.

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## 1. ATYPICAL PNEUMONIA\*†

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PRIMARY atypical pneumonia is an acute infection of the respiratory tract, presumably transmitted from person to person by contact, droplets or droplet nuclei. Any consideration of the disease as an air-borne infection, however, is subject to certain limitations. Atypical pneumonia may be one disease or it may be several diseases; it may be produced by one agent or by many agents; it may have only one clinical form with involvement of the lungs or it may vary from the mildest of infections of the upper respiratory tract to the most severe and fatal pneumonia; it may spread only by direct and intimate contact with cases and carriers, or it may be air-borne in the truest sense.

But, in spite of this lack of knowledge and this uncertainty, atypical pneumonia is worthy of mention at this symposium because it is by far the most important type of pneumonia in the Army—constituting, in our experience, a high percentage of all forms of pneumonia—and because it serves as a point of reference for investigation of the relatively enormous group of respiratory illnesses of unknown etiology.

*What Is Atypical Pneumonia Clinically?* Atypical pneumonia usually begins gradually with headache, malaise, fever, and chilliness. The throat may be dry and “scratchy” but the local upper respiratory

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† The 12 papers on air-borne infection which follow in the present and succeeding issue of this journal (6 in each issue) were given at a Symposium on Air-borne Infection before the 45th general meeting of the Society of American Bacteriologists in New York, May 3, 1944. Dr. Alexander Hollaender, of the National Institute of Health, was convener. Clinical features of atypical pneumonia, and features of the epidemiologic behavior of meningitis, mumps, chickenpox, measles, scarlet fever and streptococcal infection complicated by rheumatic fever are given clarifying discussion. Application in several areas of a wholly new method for control of infection, namely mass chemoprophylaxis with sulfonamide drugs, is recorded. The known methods of environmental control of air-borne infection, *i. e.*, ultraviolet irradiation of confined air, the addition to confined air of germicidal vapors, and finally dust-suppressive measures, are each considered, and progress is indicated in the development of equipment and in specifications of design for practical installations. These papers reflect substantial gains toward the development of a practical art of air sanitation since the subject of air-borne infection was last comprehensively reviewed in 1942 in the A. A. A. S. volume on *Aerobiology*.

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symptoms—running nose, weeping eyes and sore throat—are usually absent in the early stages. A dry, irritating cough, sometimes paroxysmal in nature, develops soon after onset and may be accompanied by substernal discomfort. Physical examination early in the disease ordinarily reveals little except mild inflammation of the upper respiratory passages.

Up to this point, then, there is little in the history or physical findings to differentiate this illness from “bronchitis” or a severe “chest cold.” But if a roentgenogram of the chest is obtained, a pulmonary shadow indicative of infiltration will be seen in the large proportion of the cases. Such a radiographic lesion is the one objective criterion required by most authorities to establish the diagnosis of atypical pneumonia.

As the disease progresses, the cough becomes productive. Physical signs of involvement of the small bronchioles appear in the chest. The majority of the patients are only moderately ill for 3 to 8 days. Convalescence is ordinarily prolonged but uneventful, and recovery is the rule.

The above description characterizes the usual case of atypical pneumonia. Variations in this picture, however, are extreme. Some patients may be sick for weeks, and develop secondary bacterial infections or other complications. Others—perhaps more important to this discussion—may have such a mild illness that they continue to work and the disease is only detected by radiographic examination. Still another group of cases warrants emphasis at this point, since it may provide one of the keys to the solution of the problems of common respiratory disease. The group has been termed “suspected atypical pneumonia” and includes cases like those described above, except for the absence of a pulmonary lesion by roentgenogram. The patients are less severely ill, but physical signs indicate pulmonary involvement. This group of cases seems to lie midway between atypical pneumonia and undifferentiated acute respiratory disease, without sharp border lines between the 3 groups.<sup>6</sup> Undifferentiated acute respiratory disease presents the big problem in respiratory disease, since its incidence is many times greater than that of atypical pneumonia.

*What Is Atypical Pneumonia Etiologically?* The answer to this question is still unknown. A similar clinical syndrome may be produced by certain bacteria, fungi, rickettsiæ and known viruses. But these well-recognized agents can be excluded with reasonable certainty in the great majority of cases.

The search for new agents has not been neglected. A number of investigators<sup>1,2,3,6,7,8,10,12,13,15</sup> have reported the isolation of viruses from cases of primary atypical pneumonia. These agents have been obtained by inoculation of ferrets and mice, mongooses, chick embryos, cats, cotton rats, guinea pigs and mice, after preliminary growth in tissue culture.<sup>11</sup> Thus far, however, a clear-cut relation between one of the agents and the human disease has not been established.

Two recently described serologic tests—cold agglutinins for human

R.B.C.<sup>9,14</sup> and agglutinins for an indifferent streptococcus<sup>13</sup>—are of some help in diagnosis, but have given thus far no definite clues to the causative agent.

Transmission experiments in human volunteers with throat washings and sputa of patients with atypical pneumonia have been more encouraging.<sup>5</sup> Approximately 7 to 14 days after inoculation by spraying, 10 of 12 volunteers developed acute respiratory disease varying from mild attacks to moderately severe illnesses during which cold hemagglutinins appeared in the sera of 3 cases. This experiment provides some evidence that atypical pneumonia is an air-borne infection.

*How Does Atypical Pneumonia Behave Epidemiologically?* Since its recognition, atypical pneumonia has shown no specific concentration with respect to race, sex or geographic area. The majority of the cases have been reported in adolescents and young adults, which is probably due to better facilities for recognition in this age group.

Sharp outbreaks have occurred in some of the eastern cities, in preparatory schools, colleges and military installations. Attack rates in certain of these epidemics have been high, varying from 14 to 40%. The incidence in contacts has also been high, and case-to-case spread has been apparent.

In contrast to this picture, however, the ordinary occurrence of atypical pneumonia in the Army is endemic or sporadic. Cases appear in the various organizations as if they were distributed at random, with the single exception of hospital personnel, where the incidence is significantly greater and concentration of cases can be demonstrated.<sup>6</sup> A further interesting, and perhaps significant, correlation has been noted between the incidence of atypical pneumonia and that of acute undifferentiated respiratory diseases.<sup>4</sup> The relationship of one to the other is relatively constant and both show seasonal variations. Both also occur with greater frequency in new recruits than in "seasoned" troops.

*How Is Atypical Pneumonia Related to the Problem of Undifferentiated Respiratory Disease and to Air-borne Transmission?* The manner of spread of atypical pneumonia will probably not be finally elucidated until the causative agent is isolated and the susceptibility and resistance of the host can be determined. A working hypothesis, however, can be employed, and one has been postulated by a number of investigators from different types of data. It seems reasonable to consider atypical pneumonia as a more severe form, with pulmonary involvement, of undifferentiated acute respiratory disease. In support of this theory are the following observations: (1) The gradation of types of clinical illness. (2) The epidemiologic relationships between atypical pneumonia and other undifferentiated respiratory illness. (3) The production of varying types of respiratory illness in human volunteers.

Proof must await further etiologic studies, but if these relationships hold true, the "disease" now called "atypical pneumonia" may constitute a large part of the problem of respiratory illness.

Thus far, no intermediary vectors, such as food and insects, have



been incriminated for atypical pneumonia. Contact, droplet and air-borne methods of transmission appear to provide the manner of spread. The only measures of control which appear to be hopeful are those to be discussed in this symposium for preventing air-borne transmission. If such measures can be shown to be effective, further information of the true nature of "atypical pneumonia" will undoubtedly be obtained.

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## 2. FACTORS IN THE CONTROL OF THE SPREAD OF ACUTE RESPIRATORY INFECTIONS WITH REFERENCE TO STREPTOCOCCAL ILLNESS AND ACUTE RHEUMATIC FEVER\*

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RHEUMATIC fever is not an air-borne disease but, since attacks of acute rheumatic fever are preceded by hemolytic streptococcus infec-

\* The views represented in this paper are those of the authors and do not necessarily reflect those of the Navy Department.

tions in almost every instance, the factors concerned in the spread of hemolytic streptococci are of equal importance in the epidemiology of rheumatic fever.

In any attempt to evaluate the importance of air-borne spread of respiratory illness or to assess the effectiveness of control measures, it is necessary to consider the whole epidemiologic pattern. Respiratory infection spreads from person to person through the air, but the amount of infection which will develop depends on the immune status of the recipients. If accurate knowledge of this receptiveness to infection after exposure in the given population is lacking, differences in morbidity may be exaggerated or minimized beyond their true weight.

Certain of these important host factors and also environmental differences were studied at the U. S. Naval Training Station at Newport, R. I., in the winter and spring of 1940 and 1941, and are the subject of the present paper.

The acute infections of the upper respiratory tract which are encountered in military populations may be divided broadly into 3 categories:

1. The contagious diseases of viral origin (mumps, measles, German measles, and chickenpox). Here, the diagnosis is easy to establish.

2. Bacterial respiratory diseases (those caused by the hemolytic streptococcus, pneumococcus, diphtheria bacillus, and meningococcus). In 1940 and 1941 at Newport, streptococcus infections were the only important group in this category.

3. Acute respiratory infections presumably of non-bacterial origin (some of these are called coryza, others have the clinical characteristics of atypical pneumonia, and in certain cases, usually in epidemic periods, the virus of influenza A or B is isolated). In the Navy, febrile respiratory infections without distinguishing diagnostic criteria are usually classified under the blanket diagnostic term, "catarrhal fever acute."

Because immunity to catarrhal fever is not the same as protection against scarlet fever or measles, and because streptococcal infection shows different characteristics of spread than non-streptococcal illness, a differentiation of the total respiratory illness into at least the 2 components, streptococcal and non-streptococcal, is necessary in order to study the epidemiologic characteristics of the diseases and the reaction of the population to these infections.

Figure 1 gives the weekly rates at Newport for visits to the dispensary with respiratory complaints, largely colds and coughs, for admissions with a diagnosis of catarrhal fever and for all admissions for streptococcal infections of which the majority were acute tonsillitis and scarlet fever.

The sharp rise of colds and catarrhal fever in December represents a wave of illness which was probably influenza A. At least the virus was isolated from many parts of the country in the epidemic which was nationwide at that time. The fact that the steep rise of catarrhal fever was paralleled by a similar increase of colds to even higher levels, suggests that the virus was widespread at this early phase of the epi-

demic and that it caused more infections not requiring hospitalization than febrile illness admitted as catarrhal fever acute.

Streptococcal illness assumed a different curve. Here, there was a straight line trend culminating in a peak in late March. Throat cultures for hemolytic streptococci were only started toward the end of the epidemic, so diagnosis throughout most of the period of observation was on a clinical basis. Without laboratory diagnosis such as throat culturing, catarrhal fever has a tendency to change its character under the same name. Probably in the early winter it was a true influenza, but the plateau effect of the catarrhal fever in the late winter months suggests that streptococcal pharyngitis and tonsillitis were here included under the diagnosis of catarrhal fever.

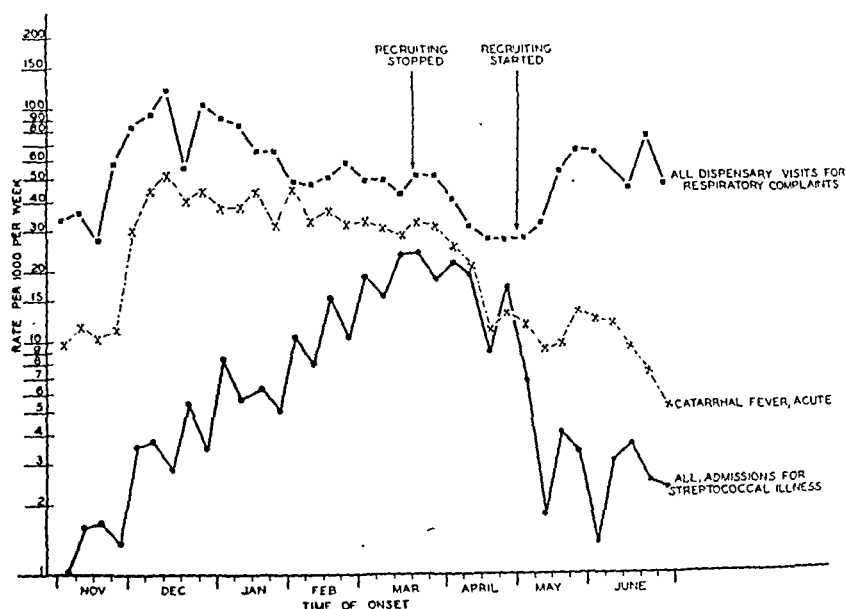


FIG. 1.—Weekly incidence of dispensary visits for respiratory complaints and admissions for streptococcal and non-streptococcal respiratory illness.

Nothing in this chart suggests that the influenza predisposed to secondary invasion by the hemolytic streptococcus. The peaks of the 2 epidemics were 12 or more weeks apart, and with a training period of 7 weeks few recruits were found to have been on the station during both epidemic periods.

Scarlet fever showed such a high incidence in the month of March that recruit reception was suspended for a period of 6 weeks. Following the stopping of recruiting, rates for colds and catarrhal fever dropped off precipitately. A few weeks later, this was followed by a drop in the incidence of streptococcal infection. This serves to emphasize one of the most important determining factors in the genesis of epidemics which is the rate of overturn of the population. It is a verification of the experimental findings of Webster in *S. typhi-murium* epidemics in mouse colonies; that epidemics are a function of the rate

of introduction of susceptibles into an infected herd. Newport had a weekly increment of 400 new recruits into a population of 2500 to 3000 from which an equal number were graduated every week. When this flow of susceptibles was cut off, it was associated with an abrupt decline in the incidence of these diseases.

As a control measure for the curtailing of epidemics, restriction of the flow of recruits should be effective; but this is a heroic measure which would hardly be practicable under present wartime needs of manpower.

The much higher respiratory morbidity in the recruit population than in the permanent personnel living in the same environment can be seen in Figure 2. This is an indication of the relatively greater susceptibility of men entering military camps from civilian life over those of greater Navy age who have undergone the physiologic conditioning and natural immunizations contingent on Naval experiences.

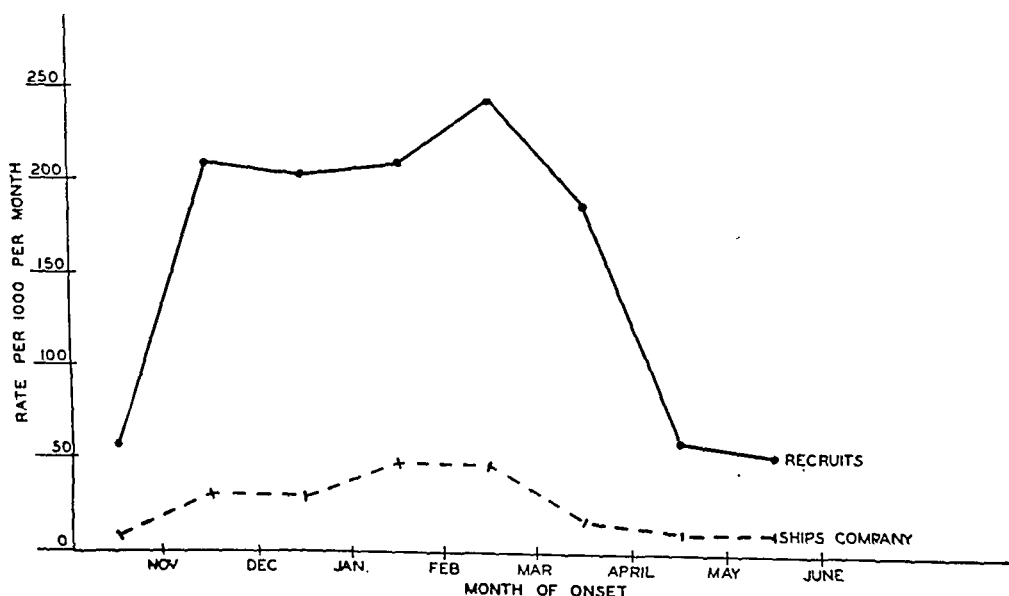


FIG. 2.—Monthly incidence of acute respiratory illness among naval recruits and ship's company (permanent personnel).

Evidence of one specific immunization through exposure was seen by the higher levels of immunity to scarlet fever, as measured by the Dick test in the Ships Company over the recruits while within the recruit population. A 15% reversal of the Dick test was demonstrated after 6 weeks in training during the period of greatest prevalence of streptococci and streptococcal illness.

Illness rates, in terms of Navy age or weeks on station before onset of disease, are shown in Figure 3. Here, the sequence of events would seem to be: a cold in the first 2 weeks, the risk of contracting catarrhal fever rising to a peak at about 4 weeks and falling off symmetrically. Streptococcal infections, apparently, required more time to build up their highest incidence. Perhaps this was due to the necessity of

repeated doses and exchange of organisms before effective exposure was established, or perhaps to the predisposing effect of the non-specific respiratory infections, although only a small percentage of the cases represented on these curves are recorded for more than one dispensary visit or hospital admission for respiratory disease.

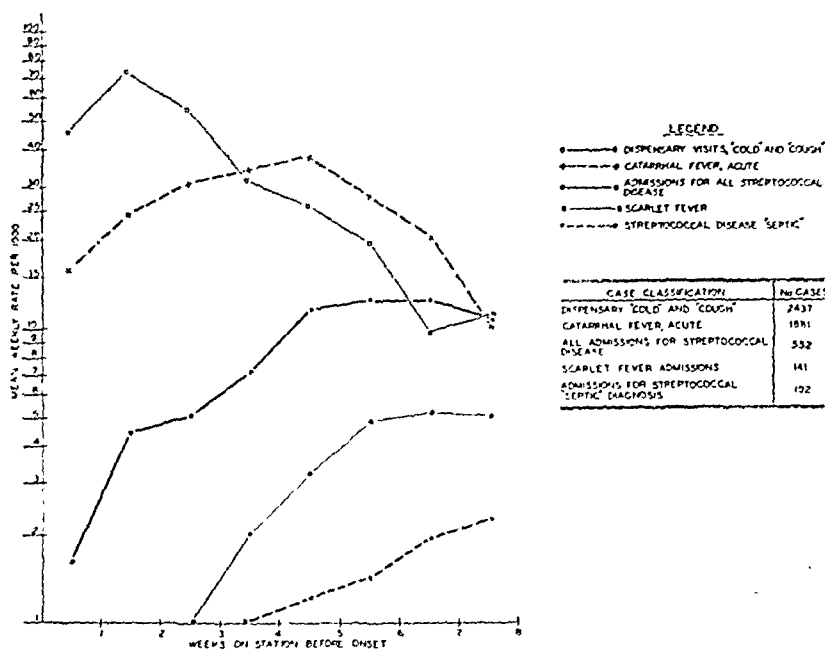


FIG. 3.—Incidence of respiratory infections by number of weeks on station before onset. Rates on basis of population spending given number of weeks in training.

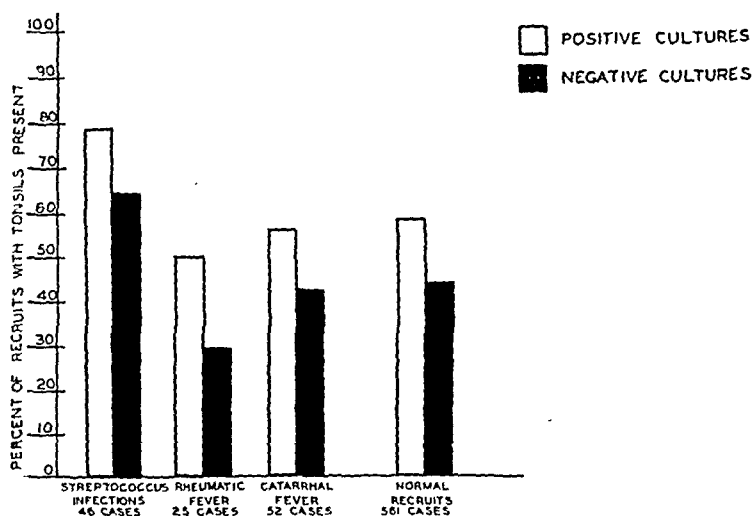


FIG. 4.—Relative percentage incidence of tonsils among recruits with positive and negative throat cultures for hemolytic streptococci in respiratory illness and in the normal population.

The fundamental importance of this factor of time on station or so-called "navy age" can be seen when controlled studies are set up

in such environments to assess various measures for the prevention of air-borne disease. Two groups of recruits alike in all respects, except weeks in training, would show marked differences in morbidity because of this factor alone.

Carrier rates for streptococci have value as an index of the air-borne spread of infection. In the recruit population at Newport, Group A streptococci were prevalent throughout the station at the time of the scarlet fever epidemic and for some weeks following. The Group A carrier rate was 53%, with 65 to 70% of the positive cultures carrying the epidemic strain, Type 6.

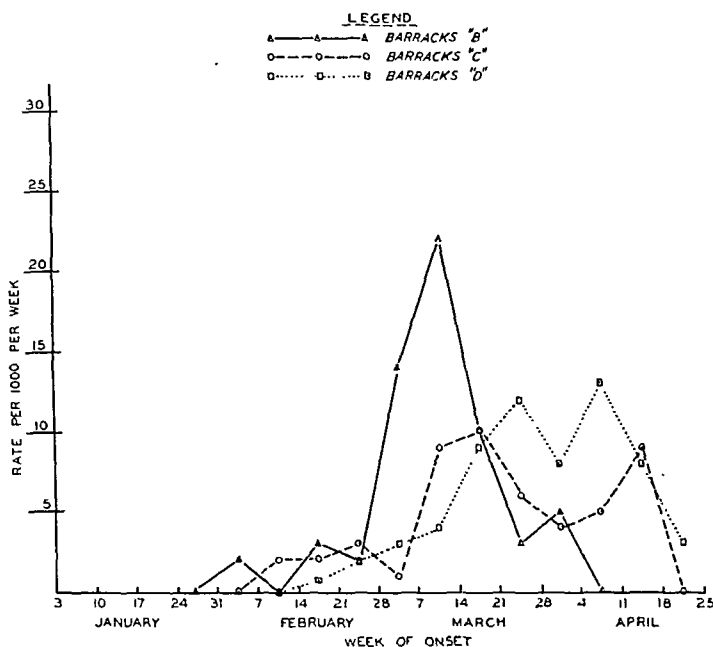


FIG 5.—Weekly incidence of scarlet fever by barracks

One host factor was found to have an influence on the carrier state, namely, the presence of tonsils. As can be seen in Figure 4, tonsils were associated with the carrier state and also with streptococcal disease. These associations were found to be beyond chance expectation in the group of 700 or more recruits whose illness and culture records were considered in terms of the presence or absence of tonsils.

The contrast of these findings with observations in the childhood age groups might be explained on the change from the lymphoid structure, often with local protective effect in the child, to the cryptic body of fibrous tissue in which is the usual adult tonsil. This latter is probably an excellent lodging place for the hemolytic streptococcus in the adult throat.

The environment of barracks or sleeping quarters was found to have a strong influence on respiratory illness, especially streptococcal infections.

At the time of this study, recruits spent a 3 weeks' detention period in Barracks "D." Following detention the companies were distributed

alternately into Barracks "B" or "C" for 4 weeks further training. Barracks "B" and "C" housing recruits in the same stage of training offered an interesting comparison because of differences in the physical environment. Overcrowding took place to a greater degree and ventilation was much less satisfactory in Barracks "B."

Figure 5 shows the weekly incidence of scarlet fever in each of the 3 barracks. Not only the scarlet fever but all other streptococcal infections without the accompanying rash showed well-defined epidemic features in Barracks "B" which were not so evident in the better ventilated and less crowded "C" barracks.

Bacteriologic sampling of the barracks air was carried out and the importance of poor ventilation and overcrowding in the spread of infection was borne out by highest total colony counts of air samples from Barracks "B" and the frequent isolation of the epidemic strain Group A, Type 6, from the air in this barracks.

**Summary.** All the factors mentioned seem to fit into 3 attributes mentioned by Dudley in his formula to express the influences controlling respiratory morbidity.

1. The rate of change or overturn of the population.
2. Environmental factors, crowding, ventilation, dust, and so on.
3. Susceptibility of the herd (this is determined by the proportion of susceptibles among new arrivals, age, rural or urban background, and so on). Among those already within the semi-closed military environment, the immune status would depend on recent previous experience with infection on the station.

Obviously, all these factors are not subject to the application of control measures, but a knowledge of their relative importance in the given population allows for a more accurate analysis of the effect of those measures which can be applied.

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### 3. SCARLET FEVER AS AN AIR-BORNE INFECTION

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THE epidemiology of scarlet fever is essentially that of the Group A beta-hemolytic streptococci which cause the disease. The members of this group are divisible into more than 40 serologically distinct types. Practically all strains are capable of inducing local infections in the throat and adjacent structures of the respiratory tract. In addition, some strains are capable of elaborating toxins which produce the rash and other systemic disturbances of scarlet fever. When

Group A streptococci reach the nose and throat of a person with an inadequate antibacterial immunity, local infection of these tissues occurs. If the invading strain of streptococcus is one which does not produce the erythrogenic toxins, the patient will not show the rash and other toxic symptoms of scarlet fever, but will develop what is usually called streptococcic tonsillitis. If, however, the invading streptococcus is capable of toxin production, there are two possibilities. If the host does not possess an adequate titer of antitoxin circulating in his blood, he will, in addition to the localized throat infection, also develop the rash and other toxic manifestations characteristic of scarlet fever. On the other hand, if he does have sufficient antitoxin, no rash will appear and he will undergo an infection which does not differ in any way from that which is caused by the invasion of a Group A streptococcus which does not produce toxin.

The ability of various types and strains of Group A streptococci to spread from one individual to another varies greatly. Some strains spread readily in a population group, while others do not. This variation was illustrated in a study of a group of 400 recruits at the Bainbridge Naval Training Center during January and February, 1944. Table 1 shows that 10% of the newly inducted men harbored Group A streptococci which belonged to 15 different recognized types. During the 6 weeks' training period only 4 types, 1, 17, 18 and 19, spread widely among the men, while the remaining 11 did not.

TABLE 1.—PERCENTAGE OF MEN\* CARRYING GROUP A STREPTOCOCCI AT BEGINNING, MIDDLE, AND END OF TRAINING PERIOD†

Type of streptococci	Beginning of training period (%)	Middle of training period (%)	End of training period (%)
1 . . . . .	0.5	5.0	9.8
3 . . . . .	0.3	0.3	0
4 . . . . .	0.3	0	0
5 . . . . .	0.5	0	0
6 . . . . .	0.5	0	0
11 . . . . .	0.5	0	0
17 . . . . .	0.3	3.5	6.8
18 . . . . .	0.5	5.8	10.0
19 . . . . .	4.0	21.3	43.8
22 . . . . .	0.5	0	0
29 . . . . .	0.3	0.5	0.3
30 . . . . .	0	0	0.5
32 . . . . .	0.3	0	0
34 . . . . .	0.3	0	0
35 . . . . .	0	0.3	0
40 . . . . .	0.3	0	0
43 . . . . .	0.3	0	0
44 . . . . .	0	0.3	0
NT‡ . . . . .	1.0	0.5	0.8
Total A . . . . .	10.0	38.5	61.8

\* 400 men comprising 3 companies.

† Training period equals 6 weeks.

‡ Non-typable.

The qualities of a strain of streptococci which determines its dispersability are not known. However, certain factors which influence



this property have been studied. For example, the rate of dispersal of Group A streptococci is greatly influenced by the season of the year. During the summer and fall these organisms do not spread readily from man to man, whereas the spread during the winter and early spring is very great. This is indicated in Figure 1, which shows the percentage of recruits at the Bainbridge Naval Training Center harboring Group A streptococci in their throats during various months of the year beginning in April, 1943. It will be seen that the carrier rate for these organisms was 54% in April, 1943, but that it dropped to 10% during June and to 4% in August, 1943, and remained around 5% until November. It then rose to 10% in December, 18% in January, 54% in February, 18% in January, 1944, and to its peak of 54% in February. A sharp decline again occurred after this to 20% in April, 1944. The monthly incidence of streptococcal respiratory infections corresponded with the carrier rate at each point.

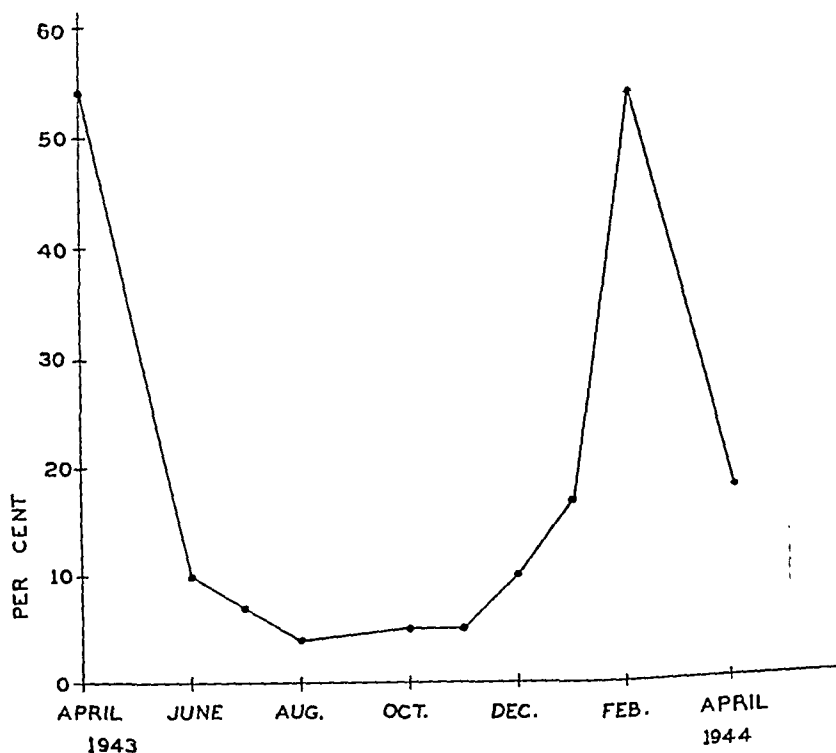


FIG. 1.—Percentage of men carrying Group A Streptococci (average monthly carrier rate)

Since recruits are housed in barracks which offer better opportunity for the spread of streptococci than exists in civilian life, it would be reasonable to expect that the percentage of men harboring these organisms would increase during their stay at the Training Center. As Figure 2 indicates, a rise in the carrier rate actually did occur among men trained during the winter, but no such increase was observed in companies of recruits trained during the early fall. Figure 2

shows the percentage of men carrying Group A streptococci at various stages during their stay at the Bainbridge Naval Training Center. The solid squares represent Group A carrier rates among 400 recruits (3 companies) at various stages during their training period in September and October, 1943. The solid circles represent the rates in 3 companies trained during January and February, 1944. On entrance to the Training Center the carrier rate for Group A streptococci was about 10% in each group. However, the rate rose rapidly among the men in camp during the winter, reaching 38% at the end of 3 weeks and 62% at the end of 6 weeks' stay at the Training Center. On the other hand, the carrier rate among men trained in the fall did not rise during their stay in camp, but remained below 10% throughout the 8 weeks they were under observation.

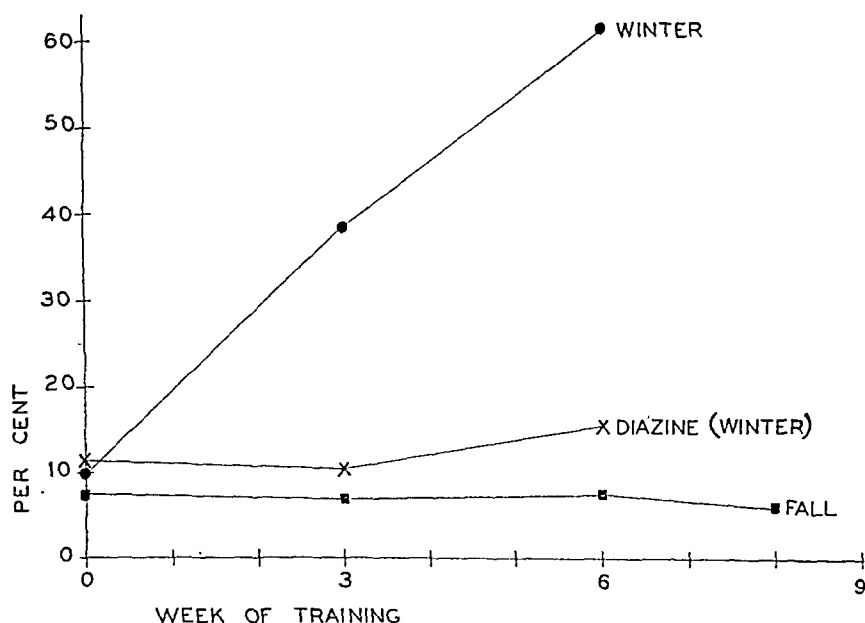


FIG. 2.—Chart showing that the rise in Group A Streptococcic carrier rate which occurs during the training period in winter does not occur during the fall and that it is prevented in winter by sulfadiazine.

The incidence of streptococcal infections in the 2 groups paralleled the Group A streptococcal carrier rate in the 2 groups of men. Thirty-six per cent of the group of men studied during the winter contracted respiratory infections of proven streptococcal etiology. In contrast, the group trained during September and October showed a streptococcal illness rate of only 7% during the 8 weeks they were under study.

It seems clear that Group A streptococci spread much more readily from man to man during the winter than they do in the early autumn, and that a corresponding difference in the incidence of streptococcal respiratory infections probably depends upon this difference in the dispersion rate during the 2 seasons.

The rise in the Group A streptococcal carrier rate which occurs during the winter under normal conditions can be prevented by the daily administration of 1 gm. of sulfadiazine as a prophylactic agent. The crosses on Figure 2 represent the Group A streptococcal carrier rate of 400 recruits who received such medication. There was very little rise in the carrier rate for these organisms during their 6 weeks' stay in camp, although this period extended from the beginning of January to the middle of February, 1944, during which time the carrier rates in control companies reached their peaks. Corresponding with the low carrier rate among men receiving sulfadiazine, a very low streptococcal infection rate was observed.

The mechanism involved in the reduction of the spread of streptococci from man to man by sulfadiazine is not known. The bulk of evidence indicates that the drug is not very efficacious in clearing these organisms from the throat of a carrier. Presumably, streptococci do not become established in the throats of men receiving sulfadiazine so readily as they do under ordinary circumstances.

The mechanical means involved in the spread of Group A streptococci from individual to individual is not well understood. It is known that outbreaks of streptococcal throat infections due to contaminated milk and other foods have occurred, but in the main, streptococcal infections appear to be air-borne. Inhalation of these organisms, with subsequent invasion of the nose and throat of susceptible individuals, is probably the usual mode of spread.

It is known that streptococci are exhaled into the air by normal carriers or by persons suffering from streptococcal respiratory infections. For example, on several occasions we have recovered streptococci on cough plates held at a distance of 2 feet from the mouth of a scarlet fever patient. When this distance was exceeded, no streptococci were recovered. Similarly, we have several times grown streptococci upon blood agar plates exposed for 1 hour at the bedside of scarlet fever patients. We have failed, however, on a number of occasions to recover streptococci from samples of room air taken at a distance of 10 to 15 feet from patients with scarlet fever. Numerous attempts to recover these organisms from the air in a room housing 400 men, many of whom were carriers of Group A streptococci, also yielded negative results. These findings have inclined us to the view that streptococci are not present in large numbers in the general air reservoir, even under conditions most favorable for their dissemination. On the other hand, the evidence indicates that the concentration of these organisms in the immediate vicinity of persons harboring them is quite high. It is probable, therefore, that the chance of infection is greater the nearer a susceptible individual is to a person who is exhaling streptococci. This does not mean that streptococcal infections are not, in the main, air-borne, but that the radius of initial spread may be a relatively limited one due to the fact that these organisms settle rapidly to the floor. Once the streptococci reach the floor they may adhere to particles of dust and again become a hazard at any time that air turbulence causes them to float again. Since streptococci are

resistant to exposure, this process may be repeated many times during the life of the organism. Nevertheless, it is known that dust settles more or less rapidly so that the total period of time the organism is actually air-borne and thus a hazard may not be great. Humidity, the type of dust, the nature of the floor covering, the amount of movement in the room and many other factors influence the rôle of the air reservoir in the dissemination of organisms.

To summarize our views on this matter, we believe that streptococcal respiratory infections are usually air-borne. Infection is most likely to occur in close proximity to a carrier or patient by the inhalation of streptococci from the upper respiratory passages of such individuals. Infection by inhalation of streptococci from the general air reservoir of a room is a definite but probably less important factor in the spread of streptococcal disease of the respiratory tract.

**Summary.** 1. Most strains of Group A beta hemolytic streptococci are capable of producing disease. They differ widely, however, in their abilities to disseminate in the host population. The amount of illness caused by each strain is proportional to its disseminating ability.

2. Disseminative ability is influenced by climate. It is low in summer and fall and high in winter and spring. It is markedly reduced if sulfadiazine is administered prophylactically to the host group. The mode of action of the drug seems to be to prevent implantation of the streptococci in the respiratory passages.

3. Cross-infection with streptococci occurs by direct air-borne transmission from a carrier or patient to another individual, or less directly by inhalation of streptococci floating in the general reservoir of air. Of these two, the former method is probably the more important.

#### 4. THE TRANSMISSION AND CONTROL OF MENINGOCOCCAL INFECTIONS\*

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THE meningococcus can frequently be found in the nasopharynx of apparently normal individuals who, in so far as is known, have not had any contact with clinical meningococcal infections. These persons have been generally called "carriers." Glover has suggested

\* These investigations were aided by the Commission on Meningococcal Meningitis, Board for Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of the Surgeon General, War Department.

that a "non-contact carrier rate" of 20% or more is a danger signal which presages the occurrence of cases of cerebrospinal fever. However, Dudley and Brennan, among others, have found high "carrier rates" in populations where clinical meningococcal infections were not occurring. Maxcy and Dingle and Finland, in their reviews, have questioned the importance attached to crude carrier percentages. Also, it has not been fully appreciated that the presence of large numbers of nasopharyngeal "carrier" infections during outbreaks of meningococcal meningitis, while required, must be accompanied by other essential conditions. In other words, during periods of unusual prevalence the "high carrier rates" comprise only a necessary but etiologically insufficient condition.

The term "carrier" has many connotations which interfere with a clear understanding of the host parasite relationships. It can be interpreted to imply that the individual may act as a passive vector. It is difficult to concede, however, that living animal tissue can be the site of multiplication of any organism without reacting in some way to its presence. The reaction to such multiplication may be so slight and transient as to escape recognition and be discernible only by an altered response of the host tissue such as antibody formation. It may be so severe as to be obvious to all observers. Reactions in all possible gradations must be considered "infections."

Individuals harboring the meningococcus in their nasopharynx are said by Netter and Debré to exhibit a local reaction to its presence. This observation has not been satisfactorily confirmed. The consensus at present does not accept any distinct specific inflammatory reaction. Whether an antibody response occurs among this group is unknown because the methods available are too crude and complicated. Specific bactericidal activity has been obtained with sera of apparently normal individuals who, to their knowledge, have not had a previous meningococcal infection.

There is no reason to believe that the ecology, with respect to man, of the meningococcus differs from that of *C. diphtheriae*, *H. influenzae*, *Streptococcus pyogenes* and others. The classification of "carriers" as infected individuals implies that the clinical syndromes, nasopharyngitis, meningococcemia, or meningitis, are expressions of the degree of invasion rather than any fundamental difference in host parasite relationships. With this concept, cases can be considered uncertain and irregular indicators of the spread of meningococcal infections in a population. The real flow is submerged and can be revealed solely by uncovering subclinical infections.

The Commission on Meningococcal Meningitis arranged an investigation during the spring of 1943 at a large Army camp, (1) to describe the dynamics of subclinical meningococcal infections, according to type, in respect to distribution, prevalence, incidence and duration; and (2) to determine the minimal effective dose of sulfonamides required to obtain parasitic cure of these infections. The size of the samples, the interval between cultures, and the techniques employed were so planned as to furnish valid answers.\*

\* A detailed report with bibliography appeared in the *Am. J. Hyg.*, 40, 318, 1944.

The results of this investigation disclose several important aspects of the dynamics of subclinical meningococcal infection among Army personnel. The average composite prevalence rate was 40%. Of the 99 men in the group, 92.9% were infected at some time during the study period. Of the 92 positive men, 44 had infections classified as "persistent" under a reasonable definition. An approximately equal number had only "transient" infections. Classification of the plates according to the type and number of meningococcal colonies present did not differentiate between the "persistent" and "transient" infections.

No correlation could be demonstrated between the daily prevalence rates, climatic conditions, the occurrence of upper respiratory diseases and the incidence of the common contagious diseases, including clinical meningococcal infections.

No fixed pattern could be derived from the study of the individual records. Some men were negative throughout the study period. Spontaneous parasitic cures occurred in many. In others, infections with one type would be followed, interrupted, or accompanied by an infection with another type.

The frequency distribution of meningococcal types as isolated from cases was not duplicated when subclinical infections were studied. All the clinical cases at this camp had been associated with the Group I meningococcus. Typing of the strains isolated from cases throughout the Army had shown that 91.6% were Group I. Among the 99 men in control Group "B," 53.5% of the subclinical infections were Group I, 38.4% were Type 2a and 40.4% were Group II.

The high proportion, 92.9% of the 99 men found infected, extended and confirmed the concept that the spread of the meningococcus is primarily at the subclinical level. Only 7 escaped infection during the brief period of 68 days, indicating the extent and rapidity of flow.

It is apparent that the composite or type specific prevalence rate for any given day or for the study period as a whole is a static representation of a biologic equilibrium and does not describe the rate of transmission of the meningococcus. A dynamic process exists and must be illustrated by a dynamic equation. The number of new infections in each succeeding time period, that is, the incidence rate, is a much better index than the level of prevalence attained. If the incidence is increasing, transmission is taking place; if it is decreasing, conditions are operating against the survival of the parasite. The same prevalence may be found in two population groups, yet in one there may be a declining incidence and in the other an increasing transmission of the meningococcus. If all other factors are equal, such as group susceptibility or degree of contact, the latter situation would cause more concern.

With this concept, the hypothesis of a "fixed epidemic level" of subclinical meningococcal infection fails. Glover concluded that there was a correlation between prevalence and the incidence of clinical cases by stating: "A carrier rate of 20% (without awaiting the occurrence of cases) should be regarded as a signal for prompt and effective

action." However, in the development of this thesis, he was actually concerned with the changes in the prevalence rather than the static level. In his report the following inferences were drawn: "A wave of high (non-contact) carrier rates preceded and accompanied an outbreak of cerebrospinal fever . . . there is a carrier epidemic (for the most part entirely devoid of symptoms) preceding and accompanying the much smaller case epidemic." He did not stress sufficiently the importance of this latter observation and later workers have neglected it entirely. From this and other studies of the Commission on Meningococcal Meningitis during the past 2 years, it has been evident that the number of cases would be determined by the incidence of new infections, rather than the prevalence, in any given period.

These observations also offer an explanation of the failure of control measures which have been suggested in the past. The meningococcus must be considered as an "efficient parasite" which maintains itself in any human population through infections at a subclinical level. Only a very small proportion of the total number of infections are followed by clinical manifestations. The latter group acquire the parasite, not necessarily from contact with other cases, but from apparently healthy individuals who have a subclinical infection. As there are no methods for the protection of susceptibles, a reduction in the number of clinical cases can be obtained only by decreasing the probability of exposure to the meningococcus.

Four measures have been commonly employed to interrupt transmission of a pathogen: (1) isolation of the identified infected individual; (2) the treatment of the infected individual; (3) sterilization of the medium of transmission; and (4) protection of the recipient by immunization. The first 2 have failed with the meningococcus because, despite the threshold employed, there is no feasible method of identifying all these suspected foci. For control, the entire population must be considered as the unit and attention directed toward those factors which determine the constants of the biologic equilibrium. It is almost impossible, under the conditions of human intercourse existing today, to change these factors to any appreciable extent. The possibility of reducing transmission by sterilizing the air of enclosed living spaces with aerosols or ultraviolet radiation are still being explored. The lack of any successful immunizing antigen precludes the use of the fourth method. The risk of exposure to the meningococcus can be reduced only if parasitic cure of the infected individuals in a population is obtained without resort to their specific identification.

The sulfonamides have been suggested for the eradication of the meningococcus from the nasopharynx. There are certain administrative difficulties and hazards encountered whenever extensive drug therapy is instituted. It is accepted that some individuals are or will be sensitized to sulfonamides. This usually follows repeated courses. The meningococcus, furthermore, in view of the experience with the gonococcus, may become drug-fast. One of the phases of this study was to determine the optimal dose suitable for mass administration.

The drugs were administered orally under direct supervision.

Group "A" received 1 gm. of sulfadiazine twice daily for 3 days, a total dosage of 6 gm. One and 2 gm. of the same drug were given as a single dose to the men in Groups "C" and "D," respectively. Group "B<sub>1</sub>" received a single gram of sulfamerazine.

No toxic reactions, such as rash, fever, urinary complaints, nausea or malaise, were encountered. A few noted dryness of the throat and 2 who had received 6 gm. complained of a mild headache during the course of therapy. No subjective visual disturbances were elicited. Hematologic studies and urinalysis revealed no abnormality attributable to the drugs. However, none of the men had a history of prior ingestion of the sulfonamides.

The criteria selected to assess the efficiency of the chemotherapeutic procedures were: (1) Comparative and absolute reduction of the prevalence level. (2) The length of the resultant negative interval. (3) The frequency of persistence or recurrence of infections with the same type of meningococcus.

The first of these is most easily measured and most apparent. However, the change in the prevalence level does not differentiate between suppression below the threshold of identification and eradication of the meningococcus from the nasopharynx. For this characterization, the last two indices must be employed. For their determination, the same groups must be cultured regularly for a definite period of time. They are influenced by other factors such as the incidence of meningococcal infections in the untreated group and the degree of reëxposure of the treated men. Therefore, these two criteria cannot be used for the evaluation of different studies even though the technical methods are similar.

In this trial, parasitic cure was obtained with 2 or more gm. of sulfadiazine. The 1-gm. doses of sulfadiazine or sulfamerazine were followed by parasitic cure in some and only suppression in others. This conclusion was based upon the following observations: (1) Immediately subsequent to the administration of 2 or more gm. to the 154 men in Groups "A" and "D," all the 85 known prior infections became negative. Only 1 positive result was obtained in an individual who had been negative on 4 previous occasions. When 1 gm. was given to the 103 men in Groups "C" and "B<sub>1</sub>," 5 of the 61 prior infections persisted through the first post-drug culture. (2) The reduction in the average prevalence level of Groups "A" and "D" when compared to the results of the concomitantly cultured control group exceeded 85% for the post-drug period. This reduction in Groups "C" and "B<sub>1</sub>" averaged about 60%. (3) Comparison of the average prevalence level before and after drug in Groups "A" and "D" revealed a reduction of over 80%, while that for the other groups was approximately 60%. (4) The length of the resultant negative interval when all types of meningococci were considered was 14 days for Groups "A" and "D" and 6 to 8 days for Groups "C" and "B<sub>1</sub>." Calculation of this interval with respect to the recurrence of the same type or the occurrence of new infections as manifested by change of type, revealed no material differences. (5) The maximum incidence of recurrent infections with



the same type of meningococcus in Groups "A" and "D" was 6.9% and 14.8%, respectively. In contrast, the incidence of recurrence was 43.2% for Group "C" and 38.2% for Group "B<sub>1</sub>."

The use of the sulfonamides, therefore, offers a feasible method for rapidly decreasing the prevalence of meningococcal infections in any limited group. Increasing the amount of drug given as a single dose or repeating the dosage would merely extend the period of meningococcal activity, provided an adequate level were attained or maintained.

Prophylaxis by chemotherapy, however, cannot control the incidence of reinfections indefinitely. It must be recognized that only immediate parasitic cure or suppression is obtained. There may be a brief refractory period following the administration of the drug, due possibly to a change in the nasopharyngeal bacterial flora. However, there are no grounds, either theoretical or experimental, for the assumption that the sulfonamides, except during the relatively brief period of their activity, confer freedom from, or enhance resistance to, subsequent infection over any long period of time. The rapidity with which the treated groups will attain the prevalence level of the general community will depend upon their degree of reëxposure. Exposure is a resultant of the *effective contact rate* between the treated and untreated groups and the *incidence*, as contrasted to the *prevalence*, of meningococcal infection, among the latter. Any plan for prophylaxis by chemotherapy must consider these factors, and not be determined arbitrarily.

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## 5. THE CONTROL OF MENINGOCOCCAL MENINGITIS BY MASS CHEMOPROPHYLAXIS WITH SULFADIAZINE\*

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THE proven efficacy of sulfadiazine in clearing the nasopharynx of meningococci<sup>1,4</sup> has suggested the possibility of controlling meningococcal meningitis in military and naval activities by mass chemoprophylaxis using this drug. The work of Kuhns and his collaborators<sup>3</sup> has proven this to be practicable. The present attempt to control upper respiratory infections at naval training centers by means of sulfadiazine prophylaxis has given an opportunity for evaluating the efficacy of this measure as applied to a large group of men supposedly exposed to meningococcal infections.

Approximately 600,000 men stationed at 8 training centers in the continental United States were given 0.5 gm. to 1 gm. of sulfadiazine daily during their period of training, which averaged 7 weeks in

\* This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the author, and are not to be considered as reflecting the policies of the Navy Department.

length. The majority of men received the larger dose. Somewhat smaller but otherwise roughly comparable groups at the same training centers did not receive the drug and served as controls. The total number of man-exposure days in the treated groups was considerably greater than that of the control groups. Since the rates of meningococcal meningitis for the 2 groups are not available at this time, only the actual number of cases for each are given in Table 1.

TABLE 1.—CASES OF MENINGOCOCCAL MENINGITIS IN SULFADIAZINE FIELD TRIAL UP TO JUNE 1, 1944

Activity No.	Period of observation	Treated group cases	Control group cases	Total cases
1	Nov. 5, 1943–June 1, 1944	0	1	1
2	Nov. 27, 1943–June 1, 1944	1*	47	48
3	Dec. 1, 1943–June 1, 1944	0	70	70
4	Dec. 1, 1943–June 1, 1944	0	15	15
5	Dec. 5, 1943–June 1, 1944	2†	7	9
6	Feb. 1, 1944–June 1, 1944	2*	1	3
7	Feb. 8, 1944–June 1, 1944	0	1	1
8	Feb. 18, 1944–June 1, 1944	0	4	4
Total:		5	146	151

\* These cases developed within the first 24 hours of chemoprophylaxis.

† These cases were receiving 0.5 gm. of sulfadiazine o.d.

It appeared that sulfadiazine in daily doses of 1 gm. was effective in reducing the morbidity of meningococcal meningitis to practically *nil*. Unfavorable reactions to the drug occurred in less than 0.3% of the treated group. The final morbidity figures and the details of the drug reactions observed are to be included in the complete report which is to be published shortly.<sup>2</sup>

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## 6. MUMPS AND CHICKENPOX AS AIR-BORNE DISEASES

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**Mumps.** Experimental evidence on the possibility of mumps being an air-borne disease is limited. Mumps virus has been isolated from the saliva of patients up to 48 hours after onset of the parotitis.<sup>4</sup> Monkeys cannot be infected by merely spraying the nose and throat with virus, but must be inoculated directly into Stenson's duct.<sup>6</sup>

An attempt to infect experimentally a group of susceptible humans<sup>5</sup> required repeated spraying of the throat and the placing of virus-soaked pledgets of cotton in the mouth to bring down 6 out of 13 so exposed—evidence either of low virulence of virus or of relatively low level of susceptibility.

Clinically there are no symptoms in mumps such as coughing or sneezing which would induce any large amount of droplet nuclei formation.

Epidemiologic evidence shows that mumps usually does not occur in epidemics except in aggregations of large numbers of susceptibles as in schools or military groups. The epidemics are not of the static explosive type but tend to continue throughout a whole season.<sup>7</sup> Many are exposed a number of times before developing the disease.<sup>7</sup> It is not at all unusual for siblings with intimate and prolonged exposure to a case of mumps in the household to escape infection. It has been noted that mumps occurring at the same time as upper respiratory infections tends to spread more rapidly and more widely than ordinarily because of the increased droplet formation due to the concomitant sneezing and coughing.<sup>11</sup>

In contagious disease hospitals where opportunity for direct or intimate contact is reduced, the secondary attack rate in susceptibles exposed to mumps is almost *nil* as compared to measles or chickenpox, where the rates are quite high.<sup>14</sup>

Further evidence of the relatively low degree of contagiousness in mumps, provided inapparent infections can be ruled out, is the fact that the age of peak incidence is between 8 and 9 years—the latest for any of the communicable diseases of childhood, and even at the age of twenty years, 40% of the population give a negative history of mumps.<sup>8</sup>

Experimental research with mumps as an air-borne disease is not practical, since monkeys are the only susceptible animal and even these can be infected only by direct inoculation. However, from the standpoint of clinical investigation recent work has provided means of determining the immunity status of exposed individuals other than by the history. A complement-fixation test and a skin test give promise of offering means of determining susceptibility to mumps.<sup>2</sup>

The control of mumps in civilian populations offers little difficulty. With a low mortality rate and relatively rare epidemic outbreaks, it is more of a nuisance than a problem. However, in military populations especially during mobilization, mumps can assume an important place in the causes of disability.<sup>10</sup> From the standpoint of man-days lost in World War I due to disease, mumps was second only to influenza.<sup>9</sup> The high incidence of complications, especially orchitis, adds greatly to the problem when mumps is encountered in military groups. There is evidence already that mumps represents a definite medical problem in the present war.<sup>7</sup>

The use of ultraviolet light irradiation as a means of controlling the spread of mumps in school children has been studied by Wells, Wells and Wilder.<sup>15</sup> Although they conclude that there was less spread in

irradiated as compared to non-irradiated classes, the results are not clear-cut.

On the experimental, clinical and epidemiologic evidence it is concluded that under most circumstances mumps is not a true air-borne disease.

**Chickenpox.** There is little experimental evidence one way or another as to the air-borne nature of the spread of chickenpox. Virus has been isolated from the local lesions and from the blood and humans have been infected by the intravenous and subcutaneous routes.<sup>12,13</sup>

Clinically, there are few respiratory symptoms, but lesions do occur on the mucous membranes of the mouth and throat; and the apparent respiratory spread of this disease probably depends on this, and on the fact that the virus circulates in the blood and could be thus eliminated through the respiratory mucosa even before the development of lesions. Actually, a chickenpox patient is infectious as long as 4 days before and up to 5 days after the rash appears.<sup>14</sup>

The history of chickenpox shows many epidemic outbreaks. These epidemics are usually of the static explosive type when the disease is introduced into an aggregation of susceptibles. Often just one mass exposure for but a brief period of time results in 100% of the susceptibles coming down with the disease.<sup>11</sup> There have been instances reported of cross-infection with chickenpox in hospitals by the introduction of a susceptible child into a room previously occupied by a patient with the disease. In contagious disease hospitals where the possibility of spread by contact is minimal due to isolation, cubicle technique and aseptic nursing, the pattern of spread of chickenpox is often no different from that in a comparable group of susceptible children not so protected against contact.<sup>3</sup>

The highly contagious nature of chickenpox is evident in the fact that by 10 years of age over 50% of all children have had the disease, and the age of peak incidence is 4 years.<sup>11</sup>

At the present time there are no adequate means of studying chickenpox as an air-borne disease from the experimental standpoint. Animal susceptibility has not been thoroughly investigated, and in humans there is no method of determining the immunity of an exposed individual except by history or the presence of typical scars.

Control of the spread of chickenpox is difficult, due to the fact that the patient is infectious before a diagnosis can be made, the secondary attack rates are high and at present there is no practical means of active immunization. In spite of the low case fatality rate and the relative mildness of the disease, the inconveniences to individuals and to the management of schools and institutions during a chickenpox outbreak make its control desirable.

Several reports are available as to the use of ultraviolet light in the prevention of spread of chickenpox. Wells, Wells and Wilder<sup>15</sup> have reported a marked lowering of the secondary attack rates in irradiated classrooms as compared to non-irradiated using mass irradiation. Others using curtains of ultraviolet light about hospital cubicles have had encouraging results.<sup>3,8</sup>

Chiefly on the basis of its epidemiology it is concluded that chickenpox is probably a true air-borne disease.

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### INADEQUATE ACTION OF PENATIN AGAINST BRUCELLA ABORTUS IN VIVO\*

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#### PART I

CULTURE filtrates of *Penicillium notatum*, designated as "penatin" (penicillin B,<sup>5</sup> notatin<sup>1</sup>) have been shown<sup>1 2</sup> to have a marked antagonistic action against *Brucella abortus* in vitro.

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**Method.** In order to study the activity as well as any toxic effects of penatin *in vivo* 40 guinea pigs were used. All the animals were tested and found negative to the agglutinative test for brucellosis, and then were each injected intraperitoneally with approximately 1,000,000 *Br. abortus* cells. The strain was the third anaërobic transfer of *Br. abortus* isolated from the milk of a naturally infected cow. The weights of the 40 guinea pigs before infection ranged between 400 and 560 gm., and they were weighed weekly following infection. On the same occasions the weights of 10 non-infected, untreated guinea pigs were ascertained in order to compare the changes in weight of the variously treated infected groups with those of a group of normal animals.

**Dosage.** The penatin was prepared in separate small batches by the Kaolin method<sup>3</sup> without dialysis. The activity of the different lots varied between 200 and 2000 units\* per mg., and since different batches were mixed for injection purposes, an average unit value was adopted, namely, 1000 units per mg. which is the unit value used to express dosages in this report. Different quantities of penatin were used on groups of guinea pigs, and the animals were treated once a day, each dose being suspended in 0.85% NaCl. All injections were made by the subcutaneous route.

Twenty-four hours after infection, administration of penatin was begun on the first group of 10 guinea pigs. Three guinea pigs were injected daily with 10,000 units of penatin for 5 successive days, 5 guinea pigs were injected daily with 50,000 units for 5 successive days, and the remaining 2 guinea pigs were given a single dose of 250,000 units. One week after infection, another group of 10 guinea pigs was subjected to penatin treatment. In this instance, 3 animals were injected daily with 20,000 units of penatin for 5 successive days, 5 animals with 50,000 units daily for 5 successive days, and the remaining 2 guinea pigs received a single dose of 500,000 units. The other 20 infected guinea pigs were left untreated to serve as controls. (One control guinea pig died of intercurrent disease 2 weeks after infection.) During treatment the temperatures of the guinea pigs were recorded before the injection of penatin and again several hours later.

**Toxicity.** The local toxic effects following the administration of penatin were manifested by swellings which appeared soon at the sites of injection, and which were proportionate to the quantity of the substance introduced. The guinea pigs which received 10,000 units of penatin did not show any local reactions; the guinea pigs injected with 20,000 units of penatin exhibited slight swellings, and those injected with doses of 50,000 units had considerable edematous swellings which persisted for several days, and in some instances caused sloughing of the skin. The introduction of single doses of 250,000 units and 500,000 units of penatin, on the other hand, resulted in marked edema in the subcutaneous tissue with sloughing and rupture of the skin due to pressure. However, the affected areas healed within a week to 10 days without showing signs of infection, although the open wounds were exposed to the air and to rubbing against the bottom of the cages. In addition to the local reactions, there was usually a temporary rise in body temperature following injections of the larger doses of penatin.

**Agglutinative Tests and Cultures.** Four weeks after infection with *Br. abortus* the guinea pigs were tested for the presence of agglutinins against *Brucella* antigen. The agglutinative titers ranged from 1:320 to 1:1280, and there was no appreciable difference in the agglutinin

\* One unit is the smallest quantity of penatin which will suppress the growth of *Staphylococcus aureus* in 10 ml. of tryptose agar.

content of the blood sera of the treated animals as compared with the untreated controls. Two weeks later (*i. e.*, 6 weeks after infection) 8 guinea pigs from the variously treated groups and 8 controls were killed, and the liver, spleen, kidney and inguinal lymph gland were cultured for the presence of *Br. abortus*. The agglutinative titers determined on blood samples obtained immediately before sacrificing the 16 animals were on a whole similar to the previous titers. Eight weeks after infection, blood from the remaining guinea pigs was obtained for agglutinative tests, the results of which showed in general a slight increase in the concentration of agglutinins as compared to the previous titers of the same animals. One week later, 9 weeks after infection with *Br. abortus*, all the guinea pigs were killed and their tissues cultured for the presence of *Br. abortus*.

TABLE 1.—EFFECT OF PENATIN THERAPY ON BRUCELLA ABORTUS INFECTION IN GUINEA PIGS

Guinea pig No.	Daily dosage penatin in units	No. daily doses	Treatment begun	Total quantity penatin injected in units	Average increase in weight per animal		Culture findings
					4 wks. after infection	9 wks. after infection	
1142	10,000	5	24 hours after infection	50,000	75.0 gm.	112.5 gm.	* Negative
1143	10,000	5		50,000			† Positive
1144	10,000	5		50,000			† "
1145	50,000	5		250,000			* "
1146	50,000	5		250,000			* Negative
1147	50,000	5		250,000			† Positive
1148	50,000	5		250,000			† "
1150	50,000	5		250,000			† "
1151	250,000	1	1 week after infection	250,000	57.2 gm.	129.0 gm.	* "
1152	250,000	1		250,000			† "
1154	20,000	5		100,000			* Positive
1155	20,000	5		100,000			† Negative
1156	20,000	5		100,000			† Positive
1157	50,000	5		250,000			* "
1158	50,000	5		250,000			* "
1159	50,000	5		250,000			† "
1160	50,000	5		250,000			† "
1161	50,000	5		250,000			† "
1162	500,000	1	10 non-infected, untreated guinea pigs	500,000	129 gm.	221 gm.	* "
1163	500,000	1		500,000			† "
19 infected control guinea pigs: 8 autopsied 6 weeks after infection 11 autopsied 9 weeks after infection					42.6 gm.	68.3 gm.	19 Positive
10 non-infected, untreated guinea pigs					129 gm.	221 gm.	

\* Autopsied 6 weeks after infection.

† Autopsied 9 weeks after infection.

‡ Guinea pig No. 1155 died 4 weeks after infection due to cardiac puncture for the purpose of obtaining blood.

The accompanying table indicates the dosage of penatin, the changes in the body weights of the animals following infection, and the results

of cultures of the various tissues at autopsy. The most obvious beneficial effects of the penatin therapy was observed in the general well-being of the treated animals as manifested in the gain in body weight. After the administration of penatin was discontinued the animals gained considerably in weight, and 9 weeks after infection with *Br. abortus* the average increase in weight of the treated animals was almost twice as great as that of the infected controls. On the other hand, the infected, treated guinea pigs showed only about one-half the increase in weight as compared with the group of non-infected, untreated animals. Three of the treated guinea pigs did not yield *Br. abortus* on cultures of tissues at autopsy. One of these (No. 1155) died 4 weeks after infection due to injury of the heart while obtaining blood, and the other 2 animals (Nos. 1142 and 1146) were killed 6 weeks after infection. In addition, a 4th animal (No. 1144) showed only 1 *Brucella* colony on the liver culture and none in the other tissues. All the controls were positive on cultures. In guinea pigs Nos. 1142, 1144, and 1146, treatment was begun 24 hours after infection, and in guinea pig No. 1155 1 week after infection.

**Summary of Part I.** Subcutaneous administration of various quantities of penatin to guinea pigs resulted in local reactions in the form of edematous swellings at the site of injection, which were in general proportionate to the quantity of the material introduced. However, a single injection of as high as 500,000 units of penatin did not have fatal effects. Of 20 guinea pigs infected with approximately 1,000,000 virulent CO<sub>2</sub> sensitive *Br. abortus* cells, and treated with penatin, 3 did not yield *Br. abortus* on cultures at autopsy, while all the control guinea pigs were positive. In 2 of the negative guinea pigs, treatment was begun 24 hours after infection, and in the 3rd one not until 1 week after infection. The agglutinative titers of the different animals varied, but there was no distinct difference between the treated and untreated groups. The guinea pigs treated with penatin showed an average increase in weight per animal which was about twice the gain in weight of the non-treated controls.

## PART II

On the basis of results reported in Part I it was decided to repeat the experiment, using different doses of penatin on groups of guinea pigs for longer periods of time.

**Method.** For that purpose, 80 guinea pigs were injected intraperitoneally with about 80,000 CO<sub>2</sub>-sensitive *Br. abortus*, and 24 hours later subcutaneous administration of penatin was begun in 40 of the infected animals which were divided into 4 groups.

**Dosage.** The penatin employed was prepared according to Doisy's<sup>4</sup> U-acetate method, and it assayed 20,000 units\* per mg. It was planned to treat the guinea pigs as follows:

- Group 1—10 G. P. to receive 160,000 units of penatin daily, divided into 2 equal doses.
- Group 2—10 G. P. to receive 80,000 units of penatin daily, divided into 2 equal doses.
- Group 3—10 G. P. to receive 20,000 units of penatin daily, divided into 2 equal doses.
- Group 4—10 G. P. to receive 2000 units of penatin daily, divided into 2 equal doses.

\* One unit is the smallest quantity of penatin which will suppress the growth of *Staphylococcus aureus* in 10 ml. of tryptose agar.



Each dose of the material was suspended in 2 ml. of 0.85% NaCl, and the injections were made subcutaneously at 9 A.M. and 5 P.M.

The remaining 40 guinea pigs were intended as controls.

*Toxicity.* Three animals of Group 1 died after the second injection, and 3 other animals after the third injection of penatin, at which time treatment of this group was discontinued. Within the next 48 hours 3 more animals died, and the last guinea pig of Group 1 died 9 days after treatment was stopped. One non-infected guinea pig was injected intraperitoneally with 80,000 units of penatin twice daily, and this animal died after the 3rd injection. Thus it would appear that intraperitoneal injections of penatin are as toxic as subcutaneous ones.

In Group 2, 7 animals died after the 4th injection of penatin (*i. e.*, after each animal had received a total of 160,000 units of penatin) at which time the administration of penatin to the remaining 3 guinea pigs was discontinued. One of these died 48 hours later, and 2 of the animals survived.

The noticeable toxic effects of penatin in the animals of Groups 1 and 2 were: marked edematous swellings in the subcutaneous tissue at the sites of injection, and a moderate rise in body temperature following the injections. However, the body temperature dropped to several degrees below normal several hours before death. The 2 guinea pigs of Group 2 which survived had extensive edematous swellings in the subcutaneous tissue of the ventral thoracic and abdominal region (sites of injections). The skin covering this area eventually ruptured, but complete healing of the affected tissues took place within 3 to 4 weeks.

The guinea pigs in Group 3, which were injected with 10,000 units of penatin twice daily, occasionally showed local toxic effects in the form of edematous swellings which usually disappeared within 24 to 48 hours. Sometimes there was also observed a slight rise in body temperature within 2 hours after injection of penatin, but the temperature returned to normal in a few hours. Only one animal of this group died in the course of treatment, but death in this instance could not be attributed to toxic effects of the penatin. The other 9 animals were treated for 30 days.

The animals in Group 4, which were injected with 1000 units of penatin twice daily, did not show any ill effects from the treatment, and all 10 guinea pigs were treated for 30 days.

Seventy-two hours after infection, when most of the animals in the first 2 groups had died, treatment was begun on 16 more guinea pigs from the control group. Eight of these (Group 5) were injected daily with 2000 units of penatin divided into 2 equal doses, and the other 8 animals (Group 6) received 400 units of penatin daily divided into 2 equal doses. No undesirable effects were noticed from the injections of these small quantities of penatin. The last 2 groups of guinea pigs received penatin injections during the same period as Groups 3 and 4,

and therefore were treated for 28 days. Thus the full course of treatment was carried out on:

Group 3 with 10,000 units twice daily for 30 days = total 600,000 units of penatin  
 Group 4 with 1000 units twice daily for 30 days = total 60,000 units of penatin  
 Group 5 with 1000 units twice daily for 28 days = total 56,000 units of penatin  
 Group 6 with 200 units twice daily for 28 days = total 11,200 units

*Agglutinative Tests.* The guinea pigs were tested 28 days after infection with *Br. abortus* for the presence of agglutinins against Brucella antigen. The agglutinative titers ranged from 1:25 to 1:200, and there was no appreciable difference in the agglutinin content of the blood sera of the treated animals as compared with the untreated controls. (All the animals had been tested and found negative to the agglutinative test for brucellosis prior to infection.)

*Changes in Body Weights of the Animals.* The weights of the guinea pigs before infection ranged between 300 and 450 gm., and they were weighed weekly following infection. On the same occasions the weights of 20 non-infected, untreated guinea pigs were ascertained in order to compare the changes in weight of the variously treated infected groups with those of a group of normal animals. Since the animals of Groups 1 and 2 died soon after treatment was begun, changes in their weights could not be observed. The following table presents the average increases in weight per animal in the remaining groups:

TABLE 2.—AVERAGE INCREASE IN WEIGHT (GM.) PER ANIMAL

	Weeks after infection			
	1	2	3	4
Group 3 . . . . .	10.0	26.0	38.0	74.4
Group 4 . . . . .	41.2	63.0	93.9	140.8
Group 5 . . . . .	38.6	60.0	98.8	148.0
Group 6 . . . . .	32.1	63.8	92.3	134.0
Infected untreated G. P. 24 .	42.2	61.8	97.6	153.0
Non-infected untreated G. P. .	32.4	72.4	95.5	145.0

The recorded figures indicate clearly that the guinea pigs in Group 3 averaged a gain in weight which amounted only to less than one-half the increase in weight observed in the other groups. The animals of this group received the largest non-lethal doses of penatin, and it was noticed throughout the experiment that their food intake was less than that of the animals in the other groups. The general toxic effects of the penatin (fever) and the pain associated with occasional swellings at the sites of injection must be considered responsible for the anorexia. The remaining groups of guinea pigs showed approximately equal increases in body weight.

*Cultures of Tissues at Autopsy.* All guinea pigs which died before the termination of the penatin therapy were autopsied and their tissues cultured for the presence of *Br. abortus*. Twenty-two animals died during that period, *i. e.*, all guinea pigs of Group 1 and 8 guinea pigs of Group 2 succumbed to the toxic effects of penatin, while 1 guinea pig of Group 3 and 3 non-treated animals died due to intercurrent disease. Most of these animals died during the night, and because of

the warm weather conditions their tissues were decomposed. In those instances, therefore, the culture plates were covered with contaminants and no *Brucella* could be isolated from the tissues. However, in 5 animals which were autopsied soon after death, namely 4 guinea pigs of Group 1 and 1 guinea pig of Group 2, *Brucella* was recovered from the internal organs.

Thirty-one days after infection, within 24 hours after penatin therapy was discontinued, one-half of the surviving animals in each group were killed, while the remaining guinea pigs were killed 1 week later. In each instance the spleen, liver, kidney, and inguinal lymph gland were cultured, and all but 2 animals yielded *Br. abortus* on cultures of one or more of these tissues. The 2 guinea pigs which did not show *Brucella* on cultures had ruptured stomachs at the time of autopsy which caused contamination of the internal organs, and consequently contamination of the culture plates, making isolation of *Brucella* impossible. The following table indicates the number of animals in each group autopsied after the penatin treatment was completed, and the results of cultures of the tissues.

TABLE 3.—CULTURE FINDINGS IN AUTOPSIED ANIMALS

	No. animals in group	Autopsied after penatin treatment was discontinued		Culture findings
		24 hours	1 week	
Group 3 . . . . .	9	5	4	8 positive 1 contaminated
Group 4 . . . . .	10	5	5	9 positive 1 contaminated
Group 5 . . . . .	8	4	4	8 positive
Group 6 . . . . .	8	4	4	8 positive
Infected untreated guinea pigs .	21	10	11	21 positive

In addition, 2 guinea pigs from Group 2 which had survived the first 2 days of penatin injections and had recovered from the toxic effects were killed at the same time as the second half of each of the above groups. *Br. abortus* was isolated from both animals.

**Summary of Part II.** Subcutaneous injections of 80,000 units and 40,000 units of penatin twice daily proved highly toxic for guinea pigs, and most of the animals thus treated died after the third or fourth administration of the material. A lower dosage, *i. e.*, 10,000 units of penatin injected twice daily produced local toxic effects, but did not prove fatal to guinea pigs treated for 30 days; whereas animals treated for the same length of time with doses of 1000 units and 200 units did not show any ill effects from the treatment.

The largest sublethal doses of penatin used, *i. e.*, 10,000 units twice daily, as well as the smaller doses, *i. e.*, 1000 units and 200 units twice daily, injected subcutaneously for 30 days, beginning 24 hours after infection, did not have any therapeutic effect on guinea pigs infected with *Br. abortus*. All the treated guinea pigs, with the exception of 2 whose cultures were contaminated, and all the controls yielded *Br. abortus* on cultures.

Prolonged injections of 10,000 units of penatin twice daily impaired the growth of the guinea pigs, and their increase in body weight was less than one-half that of the animals in the other groups. The animals injected with this dosage showed considerable anorexia throughout the period of treatment.

These results, as well as those published in Part I of this article, show that penatin is toxic, and when administered in sublethal doses is not effective in treating *Brucella* infection in guinea pigs.

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# PROGRESS OF MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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### LEPTOSPIROSIS

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WEIL's disease is a specific febrile spirochetal infection caused by *Leptospira icterohæmorrhagiæ*. In various parts of the world this organism is common in rats, which constitute a natural reservoir and a source of human infection. The disease is characterized by a sudden onset with rather high fever, headache, and vomiting. Jaundice is common and the urine almost always contains albumin and bile. Hemorrhages, especially epistaxis, are common, and the liver and sometimes the spleen show enlargement. Polynucleosis is present.

The disease is known by several names as leptospiral jaundice, spirochetal jaundice, epidemic jaundice, spirochætosis icterohæmorrhagica, typhus bilieux and Weil's disease.

This form of jaundice was first recognized as a distinct disease by Weil in 1886, who described it as an acute infectious disease characterized by jaundice, swelling of the spleen and nephritis. Inada and his Japanese colleagues<sup>43</sup> discovered the causative spirochete in 1915, and in 1917 injected guinea pigs with the organism. Noguchi,<sup>76</sup> who thought that the organism was the cause of yellow fever, named it *Leptospira icterohæmorrhagiæ*. Laboratory methods to diagnose this disease were introduced by Wadsworth<sup>104</sup> in 1922.

Many of the synonyms used for Weil's disease should not be used, because they give the reader a wrong impression concerning the disease. For instance, spirochetal jaundice is not an adequate term, since jaundice is present in approximately only two-thirds of the cases. Epidemic jaundice should be limited to acute catarrhal jaundice caused by a virus, which is really more epidemic in nature than Weil's disease. Leptospiral jaundice or leptospiral infections are general terms and include other types of leptospiral infections. It is true that these two latter terms do include Weil's disease, but they are not specific enough. There are other strains of *Leptospira* which produce disease in man. Technically speaking, infections caused by *Leptospira canicola* should not be called Weil's disease, since he described cases due to infections caused by *L. icterohæmorrhagiæ*. However, some authors consider *L. canicola* infections as cases of Weil's disease, but most workers consider the two infections separately and merely associate them in their writings.

In recent years a number of serologic races of leptospira have been

reported. Schüffner<sup>85</sup> distinguishes 3 human strains in Europe: (1) the cosmopolitan *L. icterohæmorrhagiæ* in rat and dog and the cause of classical Weil's disease; (2) *L. canicola*, causing specific canine disease (occasionally transmitted to man); and (3) *L. grippotyphosa*, the infecting agent in the swamp fever of Eastern Europe. He believes that the clinical (non-icteric) character, the serologic, and the epidemiologic picture (appearing in well-defined epidemics) are features which separate swamp fever from the other leptospiroses. Other important leptospiral diseases are those due to *L. hebdomadis*, *L. autumnalis*, and *L. pyogenes*. *L. hebdomadis* is the cause of 7-day fever, a disease which occurs in parts of Japan and resembles a mild Weil's disease. *L. autumnalis* has been found in cases of a disease known as "Autumn Fever" or "Hasmi." This latter disease is also found in Japan. Vervoort<sup>95</sup> (quoted by Strong), in 1932, isolated the strain *L. pyogenes* from an outbreak of pseudodengue in Medan, Java. This disease was endemic in plantation areas, and was associated with a mild rash and jaundice in most of the cases.

The spirochete causing Weil's disease, *L. icterohæmorrhagiæ*, is the type species of a genus described by Noguchi as having minute elementary spirals running throughout the body and failing to show either flagella or undulating membrane. The caudal portion of the spirochete is remarkably flexible, and when in motion the whole body seems drawn into a straight line except for the hook formation of one or both terminal portions. Propulsion seems to occur by the rotary motion of the hook, and progresses in the direction of the straight end. If both ends become curved, progression ceases. It is said to be insoluble in 10% saponin, thus differing from the other blood spirochetes. It is actively motile and often bends itself in the form of a hook, giving the appearance of the letter C when the hooks are on the same side, or the letter S. The organism varies considerably in size, averaging 6 to 14 microns. The constituent spirals are closely placed together, giving the appearance of small dots. The organism has been cultivated on Noguchi's leptospira media. It prefers a partial oxygen tension and usually grows in the narrow zone just below the surface. The optimum temperature for growth is from 25° to 30° C. Because of the universal use of Schüffner's culture media for this organism, it is important to mention its ingredients. It is composed of tap water 1500 cc., Witte's peptone 0.15 gm., Ringer's solution 300 cc., and Soven-son's solution pH 7.2. The final reaction of this peptone medium should be between pH 6.8 and pH 7.2. Three cubic centimeters of this medium are placed in a small tube and sterilized, and for use 3 cc. of rabbit's serum are added. The tubes are then heated to 56° C. for 30 minutes and incubated at 37° C. overnight. The organism can also be grown on other forms of blood agar. The leptospiræ are able to pass through the ordinary types of Berkefeld filters. Inada has obtained filtrates in which no spirochetal forms were demonstrable, but which were infective for guinea pigs. He believes, therefore, that there may be a viable, granular form.

**American and World Incidence.** Weil's disease is found in practically every country in the world, excluding countries where the temperature is always low. The disease is far more common in the tropic and temperate regions of the globe. It has been common in Japan and Egypt, and is also endemic along the North African coast and the shores of the Mediterranean, in West Africa and the Congo. Cases have been observed clinically in the Sudan. However, some workers were unable to find the disease prevalent in Egypt, Arabia or Persia.

In 1939 there appeared a review from the Netherlands by Walch-

Sorgdrager<sup>105</sup> in which 374 cases were extensively studied. The number reported in England, France and Germany runs well over 1000. It has been found to be relatively common in Denmark, Austria, and parts of South America. Walch-Sorgdrager lists 46 countries in which the disease has been described. Snapper and co-workers<sup>89</sup> report for the first time 2 human and 5 canine cases of leptospirosis in China. Lesh<sup>59</sup> gives a report of a case from Nigeria. He also states that the disease is present in the Canary Isles. This is the first time the disease was definitely proved to exist there. Gardner,<sup>30</sup> in 1940, gives a report of a classical case of Weil's disease in Melbourne, Australia. Lahiri<sup>52</sup> mentions that the disease does exist in Bombay City and cites several instances. Sixty controlled cases were discussed by D'Silva.<sup>21</sup> These cases of Weil's disease were present in and about the Andaman Islands. Some other places in the Far East, where recent reports of leptospiral jaundice with bacteriologic diagnosis have been made, include the Dutch East Indies, Borneo and the Celebes, Cochin China, Indo-China, and the Malay States.

In recent years, sporadic cases have been reported in London and Scotland, and outbreaks of the disease have been described in coal miners in Scotland, in Wales, and Northeast England; in sewer workers of London, Liverpool and Glasgow; in fish workers of Aberdeen, and in tripe workers in Glasgow.

In the United States the disease has apparently been comparatively rare. In 1935, Jeghers<sup>45</sup> reviewed the American literature, and found only 11 reported cases. In 1937, Packchianian found 32 proved cases.<sup>77</sup> Eighteen of these were from other observers, and 14 were his own. According to Ashe<sup>3</sup> in 1941, there have been reported about 35 other cases since 1937, making a total of 67 cases. In 1942, Harris<sup>37</sup> gives a total of 87 cases reported in the United States. In 1944, Senekjic<sup>87</sup> reported 30 cases of this disease from New Orleans, and these 30 cases plus the many case reports from all over the country in the past 2 years gives a total of over 100 cases reported in this country at the present time. Senekjic determined that the ratio in his series of cases was 1 case of leptospirosis to every 8445 general admissions and 1 case to every 1343 medicine admissions at Charity Hospital in New Orleans. Blake<sup>6</sup> reports a fatal case of leptospirosis in Connecticut in 1940. It was the first case ever to be reported from this State. In 1943, Bruno and co-workers<sup>10</sup> reported on the salient features of 15 cases of Weil's disease that were observed at Charity Hospital. Two of the cases had Canicola fever. Their work covered a span of  $2\frac{1}{2}$  years. Reid and Holt<sup>82</sup> report a total of 13 cases in Virginia up to October, 1941. Bloom and Walker<sup>7</sup> also reported, in 1941, 7 cases of Weil's disease in Virginia. These 7 cases were observed in this State during the past 5-year period. Jentgen<sup>46</sup> reports a case from Ohio in 1941. Lester<sup>60</sup> gives a clinical and epidemiologic report of 14 cases of Weil's disease that occurred in a single mine in north central Alabama between March, 1938 and September, 1940. The work was published in 1942. Tiffany and Martorana,<sup>97</sup> in 1942, did a serologic survey for Weil's disease on 1351 individuals. They concluded that this disease, although endemic and sporadic in New York City, seems to have been usually unrecognized. Ward,<sup>108</sup> in 1942, reports cases in poultry dressers from Baltimore.

A question which always arises when Weil's disease is discussed is—Why is the disease more common in Europe when essentially the same conditions exist here as in Europe? The reasons for this discrepancy are probably numerous. In general, our laws do not provide for a more satis-

factory elimination of rats than is carried out in France, England, and Germany, though it must be admitted that our sewage disposal systems make it less likely that the excreta of sewer rats come into contact with those employed to maintain the sewer systems. There is no reason to suppose that North Americans are immune. Meyer,<sup>67</sup> in San Francisco, has found that when Weil's disease is carefully searched for, it is not difficult to find. There are 5 main reasons why the diagnosis is missed so often: (1) American Medicine textbooks have described the disease poorly, emphasizing chills and splenomegaly, which are rarely present. (2) Most city and state health laboratories are not equipped to make the diagnosis. (3) Most doctors have considered the disease too rare to include in their differential diagnosis. (4) Few physicians are aware that only 60 to 66% of the cases have jaundice. Finally, (5) In those few laboratories in which clinicians have attempted to prove the diagnosis, they have frequently failed, because they have not been familiar with the precautions which must be taken in order to establish the diagnosis in each of the 4 distinct stages of the disease.

**Epidemiology and Endemiology.** *L. icterohæmorrhagiæ* is found in the excreta of more than 10% of adult common gray rats.<sup>45</sup> It has been found not infrequently in dogs,<sup>6,33,80,85</sup> and is known to be present in field mice,<sup>105</sup> cats,<sup>1</sup> pigs,<sup>19</sup> foxes,<sup>19,22</sup> mongooses,<sup>1</sup> minks and bats,<sup>80</sup> poultry,<sup>48</sup> in the bandicoot<sup>95</sup> and in horses. All authors agree, however, that the vast majority of known cases of Weil's disease come from direct contact with the excreta of rats.

Human infection may result from the ingestion of food or water contaminated with the urine of infected rats. The leptospiras occur in the urine, kidneys and feces of wild rodents, especially *Mus norvegicus*, *M. alexandrinus*, *M. rattus*, the mouse, *M. musculus*, and the vole of Japan. In Europe, Schüffner believes the sewer rat, *M. norvegicus*, is especially concerned.<sup>85</sup> He found all the local epidemics he studied were usually accompanied by heavy murine infections, up to 56%. He considers that human infections are the result of contamination of the water by the urine of the infected rats. The percentage of infection among older rats was found to be always greater than in the young rats. In the younger animals the infection might be 3%, while in the adults up to 45%. This agrees with the work of Larson<sup>56</sup> in this country, who trapped wild rats in and about Washington, D. C., and found a greater incidence of infection among specimens over 20 cm. in length than among those of smaller size. He found the most reliable method for the detection of the organism among rats to be serologic examinations of their sera, and studies of Levaditi-stained sections of their kidneys. It has been suggested that the disease was primarily epizootic in wild rats, but that these rodents have become tolerant and that some of them may harbor the parasite throughout life. It is regarded probable that the infection may be passed from one rat to another by way of food polluted with urine, and by sexual intercourse. Human infection may also occur from the bites of rats.<sup>48</sup> A case is reported by Varadi<sup>103</sup> where a young soldier in the British Army contracted the disease by merely handling a rat trap. This was his only contact. Lewis<sup>61</sup> gives a report on the incidence of *L. icterohæmorrhagiæ* in trapped rats in Philadelphia in 1942. He demonstrated the organism in 11 out of 100 wild rats, *M. norvegicus*. The organisms were capable of giving symptoms of a leptospiral infection in guinea pigs. Inoculation of guinea pigs from kidney emulsion technique was 90% efficient, as compared with a low per cent of "positive takes" obtained by other means.



In Bombay City in 1941, Lahiri<sup>51</sup> demonstrated leptospiras in the kidneys of 11 rats out of 125 rats trapped in the city. He used direct dark-ground illumination to demonstrate the organisms. Two other animals showed evidence of infection serologically. The rats found to be infected were all of the species *Rattus norvegicus* except 1 which was of the species *R. rattus*.

Rats carry the organisms in the tubules of their kidneys and excrete them with the urine. Soil, food, and water contaminated with rat urine can become a potent source of infection. The causative organism will live for a period longer than 3 weeks<sup>16</sup> in stagnant water which is neutral or slightly alkaline. Van'Theil<sup>102</sup> in 1937 found that during the summer season of warmer weather *L. icterohæmorrhagiæ* survived for at least 22 days after infection of the water, and that its virulence remained intact at least as long as that. Lester,<sup>60</sup> in studying 14 cases in Alabama mine workers, noticed that the hydrogen-ion concentration of the pools of water found in the mines was between pH 6.9 to 7.9. By experiments, he showed that leptospira could live a long while in water with this pH. Leptospira do not live in media that are distinctly acid, and are not found in water of pH 6.7 or less.

In some localities it is thought that dogs may constitute a reservoir of human infection. Schüffner<sup>85</sup> and Meyer<sup>67</sup> were able to isolate *L. canicola* from persons suffering from an infection resembling Weil's disease. Although doubt is expressed regarding the possibility of acquiring *L. icterohæmorrhagiæ* infection from a dog source, this question needs further elucidation. Meyer also points out that *L. canicola* was not found in the rat population, so that the host relationship of the 2 spirochetes in California is apparently the same as in Holland, rats being the source of typical Weil's disease due to *L. icterohæmorrhagiæ* and dogs the reservoir for *L. canicola*. In the rare cases of human disease in which the infection has been acquired from contact with the dog, *L. canicola* has been the infection organism. Jaundice has not been noted in Europe in this form of human disease, though Meyer found jaundice in a percentage of his dogs and in human case. The susceptibility of dogs to infection with *L. icterohæmorrhagiæ* through contact with rats and the possibility that the dog may on occasion act as an intermediate vector between rat and man have received considerable attention by other workers.<sup>6,67,68,85</sup> Using the macroscopic agglutination test, Greene<sup>33</sup> showed that one-fifth of the dogs he selected at random in southern California had positive higher incidence of infection. The rate in the combined group of 368 dogs was 29%. No immune bodies against this strain was found in 100 serologic examinations in cats, or in 426 specimens from humans. Raven,<sup>80</sup> who reported on canine leptospirosis in Pennsylvania in 1941, also gives a report on the incidence of canine leptospirosis from 1930 to 1940 in the Netherlands, Belgium, Germany, Italy, and the United States. His figures for the United States are as follows:

Place	No. examined	% positive
New York . . . . .	111	11.7
Santa Rosa . . . . .	28	14.3
San Francisco . . . . .	47	34.0
Pennsylvania (rural) (old dogs) . . . . .	105	38.1
Philadelphia (urban) (young dogs) . . . . .	50	28.0

Raven concludes from this study that since dogs excrete leptospira in their urine and there is evidence that from 11 to 38% of dogs in this country may be temporary or permanent carriers and shedders of leptospira, canine leptospirosis may become a public health problem.

The leptospira may gain entrance to man through the skin and mucous membranes, the conjunctiva, mouth and intestines. In outbreaks of the disease it has sometimes been possible to distinguish among the population certain groups of people more disposed to infection than others, and the disease has been discussed as an occupational hazard. Thus, it often occurs in people whose occupation leads them near water: barge men, wharf men, fish workers, slaughter house employees, poultry dressers, miners, garbage workers, abattoir workers, soldiers in trenches, rice field workers, in fact those who carry on their work in localities infected with rats. It is even stated that among swimmers the greatest risk is to those who swim the crawl stroke, since the possibility of oral infection is greatest in this particular method of swimming. Schüffner stresses that dissemination of the etiologic agent through water should be seriously considered. It is possibly conceded, however, that contamination of the unbroken skin with water containing the pathogenic strains of leptospira probably will not result in infection. The infection of water appears to be in no way proportional with the degree of visible contamination. Jorge (1931) reported an epidemic in Lisbon in which a leptospira was isolated from a public fountain. This indicates that the mouth and mucous membranes should be considered as important portals of entry for *L. icterohæmorrhagiae*.

In the Netherlands,<sup>105</sup> it has been shown that 91 % of the cases come from contact with water, and only 9 % from those whose occupations necessitate the frequent handling of rats. However, in the United States, most of the cases reported have been in persons whose occupations demanded working in wet places where rats were common.<sup>38,105</sup> Stimson<sup>93</sup> and Lester<sup>60</sup> report the disease in miners who work in wet mines. Cushing<sup>13</sup> reports the disease in sewer workers. Havens<sup>39</sup> in 1941 reported 7 cases of Weil's disease apparently contracted by bathing in a stream polluted by infected rats. The disease expressed itself in varying grades of severity in these cases. Five were affected mildly, 2 severely, and 1 died. The diagnosis was proven by cultural studies and serologic evidence. Davis<sup>17</sup> in 1942 also reported a case where a man 25 years of age contracted non-icteric leptospirosis while bathing in water polluted by rats. Martmer<sup>63</sup> reports a case in a child where infection occurred *via* an infected dog. Meyer reports a similar case.

Of these workers who have studied the disease in Europe, Davidson,<sup>16</sup> and Hindle<sup>41</sup> indicate that one may expect to find the disease in all rat-infested places when water is permitted to remain for a period of time. In Rotterdam, Walch-Sorgdrager mentions 71 cases that have been reported from accidental falling into dirty canals, and also from swimming in local swimming pools where the daily exchange of water is not sufficient to keep the pool clean. Smith<sup>88</sup> writes that in Aberdeen it is so common among fish workers that it is known as the "fish worker's disease." Morrissey,<sup>71</sup> reporting from Australia in 1934, tells of a very high incidence of the disease among sugar-cane cutters. Tohyama<sup>98</sup> states that the incidence of the disease among rice field workers has been lowered in Japan since the use of acid fertilizer in the fields. As mentioned before, the leptospira do not tolerate a high hydrogen-ion concentration. The work of Hindle<sup>41</sup> and Alston<sup>2</sup> brings out the fact that fish workers and sewer workers are commonly infected in London and Paris. In England, Weil's disease is now considered an occupational disease in certain industries in which wet floors are unavoidable, and industrial compensation has been paid in a fatal case. In this regard, Stiles and Sawyer<sup>92</sup> in 1942

said that leptospiral infections may be considered as an occupational hazard, providing the occupation exposes the patient to rats or dogs, or to moist materials contaminated by the urine of these animals, and provided that the illness follow such exposure by the recognized incubation period of from 2 to 19 days. He states also that compensation for this industrial infection is therefore justified. Weil's disease has now been recognized as a compensable occupational disease in fish workers in New York.<sup>27</sup>

Weil's disease does not show any definite seasonal variation. Sporadic cases may occur throughout the year. It has been noted, however, that an increased incidence may be expected during the late spring and early fall. This is probably due to increased rainfall and consequent establishment of more favorable environment for the leptospira.

There are no reports in the literature of man to man infections. Man to man infections must be rare in spite of the fact that virulent organisms may be excreted in the urine for weeks. However, in spite of the rarity of occurrence, many authors mention that this still is a contagious disease and that physicians should take no unnecessary chances, but to take the usual precautions and treat the patient as if the disease were very contagious.

Of the reported cases in this country, more than 90% were males. This striking male preponderance is also common in Europe and in Japan. Out of Senekjic's 30 cases,<sup>87</sup> only 1 was a female. Seven of the 30 were colored, and the only female was a Negress. The age incidence of these cases was from 14 to 68 years. Most of these patients were admitted to the hospital from the 2nd to the 9th day after the onset of the disease, the average being from the 4th to the 6th day.

Walch-Sorgdrager<sup>105</sup> reported 363 cases from the Institute for Tropical Hygiene in Amsterdam, 323 were males and 40 were females. Smith and Davidson<sup>88</sup> have definitely shown that this is not a sex-linked susceptibility, but purely an occupational difference. In 210 fish workers tested, there were many more women with the disease than men, and in that group the proportion of women to men in the industry was 10 to 3. The ratio of infected workers was 19½ to 3.

In children, this disease is rare. Hindle and Brown describe<sup>41</sup> a small epidemic in children in England. In this country Martner<sup>63</sup> reports the only case in a child. Walch-Sorgdrager reports the following age incidence in 370 collected cases:

Age	
1-10	11 cases
10-40	210 cases
40-60	49 cases
60 and over	15 cases
Age unknown	85 cases
Total	370 cases

Learn<sup>58</sup> states that the older the patient, the more severe the symptoms. There is definitely a higher mortality in the older age groups.

**Clinical Features of the Disease.** The clinical course of the disease may be divided into 3 or 4 stages. Different authors vary. There is no sharp line of demarcation between the several stages. However, these stages are important for diagnosis, and a thorough knowledge of the features of each stage is essential if one wishes to apply correctly the various diagnostic procedures.

The incubation period varies slightly according to different authors.

Senekjic<sup>87</sup> gives the incubation period as being between 1 and 2 weeks. The best evidence in determining the incubation period of the disease is found in accidentally infected cases among laboratory workers. Schüffner<sup>85</sup> found a range of from 4 to 19 days, with a mean incubation period of 9.5 days in all cases whether icteric or not. Inada<sup>44</sup> reports 5 to 7 days. Strong reports an incubation period of from 6 to 12 days (rarely up to 19 days). Ellenberg<sup>24</sup> gives an incubation period of 10 days, and Learn,<sup>58</sup> 1 or 2 weeks. Most all workers do agree that the length of the incubation period does not appear to be of prognostic significance.

Weil's disease is characterized by a high fever, chills, myalgia, arthralgia, prostration, jaundice, hepatomegaly, a hemorrhagic tendency, conjunctival injection, disturbance of heart function, and varying degrees of renal failure. The disease is essentially a hepato-renal syndrome. Some of the older writers consider splenomegaly to be an important finding, but all recent articles stress that the spleen is enlarged in only about 10% of all cases. In the anicteric cases, the liver damage is small; there is always, however, a hepatitis no matter how mild the infection. In the majority of cases there is a moderately severe hepatitis. Inada<sup>44</sup> found jaundice present in Japanese cases in about 60%. Greene and Farrell<sup>33</sup> in 1940, in a review of the literature on the liver and biliary tract, concluded that the pathogenesis of the icterus in Weil's disease is as yet obscure. It is not due solely to large biliary tract obstruction, as severe jaundice may occur with acholic stools. McNee<sup>65</sup> describes the morbid anatomy as showing considerable hepatic cell degeneration, granulation of the liver cells with vacuolation, pyknosis, and karyolysis. Cells with 2 nuclei and mitotic figures have also been described. He states that the mechanism of jaundice may in part be due to the hepatitis itself. In 1917, Stokes, Ryle, and Tytler<sup>94</sup> demonstrated marked inflammation of the smallest biliary ducts, and concluded that the jaundice was due to obstruction in these passages. Dawson and Hume<sup>18</sup> also in 1917 showed that in some instances there was no pathologic evidence of biliary tract obstruction. Dawson and Hume advanced the duodenitis theory of partial obstruction at the ampulla of Vater as the cause of the jaundice, but this idea is no longer held even by these two authors. One German writer, studying the liver physiology in infected guinea pigs, believed that the jaundice was due to extensive blood destruction with retention of bilirubin resulting from functional impairment of the liver, the latter due to edema of that organ. This work was based in part on the indirect van den Bergh reaction, but many workers have shown the reaction to be direct in humans. Walch-Sorgdrager,<sup>105</sup> studying European cases, show that any of the known van den Bergh reactions may take place, and that they are not predictable from a clinical study of any given cases. In a recent article by Learn,<sup>58</sup> he states that the jaundice is essentially obstructive in nature, but is not complete in many of the cases, as determined by the fact that some of the patients have only a light lemon tint to the skin and scleræ. Experimental work tends to show that this obstruction is due to the viscosity of bile and the low pressure under which it is excreted, permitting it to be reabsorbed. When the bile loses its viscid character, the flow is reestablished and the jaundice disappears. From the available material it can be seen that the mechanism of icterus in Weil's disease is not entirely established. It is probably due in large part to true hepatitis, but it may also be contributed to by hemolysis and by intrahepatic biliary tract obstruction.

The kidney lesion may be mild, moderate, or severe, and is one of the

outstanding features of the disease. The urine early shows albumin, and in severe cases frequently shows red cells, casts and white cells. Oliguria is a common phenomenon, and anuria is not infrequently a cause of death. Urea retention begins early in the disease, and may be severe, the blood urea nitrogen reaching levels of 150 mg. % or higher. When severe, it is frequently associated with acidosis, again of renal origin. Jeghers<sup>45</sup> feels that the tubular damage is usually much more apparent than is the glomerular damage, and concludes that the extent of the renal damage is often better indicated by the clinical and laboratory findings than by the histologic structure of the kidneys. It is generally conceded that the renal damage, chiefly tubular, is toxic in origin and due to the spirochetes rather than to bile; this point, however, is by no means proved.

The hemorrhagic tendency is quite variable, but is a characteristic part of the clinical picture. There are cases reported, however, where evidence of hemorrhage have been absent.<sup>105</sup> Small hemorrhages have been described in nearly every organ in the body, but are most commonly found in the striated muscle, kidney, adrenal, liver, stomach, spleen and lung. Stokes<sup>94</sup> describes hemorrhages in the meninges of the brain and cord; they are rare in the brain. A review of the literature shows that early in the disease nasal hemorrhage is most common. Jeghers,<sup>45</sup> Walch-Sorgdrager<sup>105</sup> and McNee<sup>65</sup> all agree that the hemorrhagic diathesis appears to be due to primary capillary damages, and not to any disorder of the blood and its clotting mechanism. Ashe<sup>3</sup> has demonstrated decreased red cell fragility and normal bleeding and clotting times, as well as normal platelet counts and prothrombin time. White and Prevost,<sup>109</sup> in 1941, suggest that a prothrombin deficiency along with capillary damage may be responsible for the hemorrhagic state. Clapper and Meyers<sup>12</sup> in 1943 mention that the plasma prothrombin, although appreciably decreased in amount in most circumstances, usually does not reach levels sufficiently low to account for the hemorrhagic manifestations.

The Dutch physicians have emphasized the occurrence and importance of the flushed conjunctivæ. According to many writers, the most constant and typical sign of a mild Weil's disease is infection of the eyes.

Unlike most acute infectious processes, the severe muscular *aching* associated with tenderness of the muscles, especially over the back and in the calves, has in Weil's disease a pathologic basis which is one of the primary distinguishing features of the disease. According to Jeghers,<sup>45</sup> the lesion is most frequently found in the calf. This process characteristically selects isolated fibers and only part of a fiber as demonstrated microscopically.

The incidence of meningitis in Weil's disease is unknown because lumbar puncture has not been done in most instances unless the patient had clinical evidence of meningeal involvement. Most authors feel that routine punctures are indicated and will show a high incidence of mild meningeal involvement. The symptoms and signs vary widely in severity, but differ not at all from those of other mild and severe meningitides. The spinal fluid is usually under increased pressure, and the Pandy reaction is weakly positive. The cell count may range from 10 to 3000, but usually does not go above 200 or 300. The neutrophils and lymphocytes are about equal in number. The sugar and chlorides are usually normal, and the Wassermann reaction negative. Early in the disease the organisms are said to be demonstrable in the spinal fluid.<sup>105</sup> Clapper and Meyers<sup>12</sup> in July, 1943 studied 13 cases with particular reference to meningeal symptoms and signs. In only 2 cases were there both clinical and laboratory

evidence of meningitis. In 7 there was an abnormal cellular reaction in the spinal fluid without clinical signs of meningeal irritation, and in 1 case meningismus was present without the spinal fluid showing pleocytosis. He states that the cell counts of the spinal fluid may reach 1000 or more per mm.<sup>3</sup> with neutrophils predominating early and lymphocytes later. The dextrose content of the spinal fluid is not altered, but the fluid may be discolored yellow due in part to the bilirubin present. No cases of pure spirochetal meningitis have been reported in this country.

The clinical stages of the disease are three or four in number depending on the author. I will discuss the disease in terms of four clinical stages, although I must admit that there is no absolute line of demarcation.

*Septicemic Stage.* The symptoms in this stage lasts about 3 to 7 days. Approximately two-thirds of the patients have as their symptoms, chills and then fever, nausea, vomiting, arthralgia, myalgia, frontal headache, prostration, anorexia, diarrhea or constipation. Epigastric pain and discomfort, pain and tenderness of the muscles of the legs and back, and painful ocular movements are very common. As there is often an upper respiratory infection with cough and bloody sputum this may simulate atypical pneumonia. The fever is usually high, being about 102° to 104° F. The respiration is normal or rapid, the pulse is rapid, and there is a tendency to hypotension. Senekjic<sup>87</sup> mentions that conjunctival injection was present in 50% of his cases. In this state, there are no noticeable hepatic or urinary disturbances, even though the fever is continued high. *Leptospiras* may be demonstrated in the circulating blood by means of dark-field microscopic examination, but at this stage there are no demonstrable circulating antibodies.

*Hepatic or Icteric Stage.* The duration of this stage is 7 to 10 days.<sup>87</sup> Icterus usually appears on the 6th to 7th day after onset. Some writers give the 2nd and 3rd day, and others say icterus may not be manifested until as late as the 9th day after the onset. The development of jaundice is gradual. As mentioned before, it is present in about two-thirds of all cases. The liver is enlarged, tender, and painful, and is usually about 2 fingers palpable. In Senekjic's report, 10% (3 cases) of the patients did not have an enlarged liver, but jaundice was present. In his 2 anicteric cases, the liver was palpable, and hepatitis was present in both.

The spleen is enlarged in 10% of the cases, is very soft, and when enlarged it extends 2 to 4 cm. below the left costal margin. It may be compared to the spleen seen in typhoid fever patients.

During this stage, gastro-intestinal symptoms have a tendency to subside. Vomiting, arthralgia, myalgia and headache are not particularly distressing, but the patient is usually toxic, apathetic, prostrated, and has a continuous fever. There is moderate abdominal distention due to a varying degree of ileus and diminished peristalsis.

In Senekjic's<sup>87</sup> cases, hemorrhagic phenomena were noticed in 16 cases (53.6%). There is often seen conjunctival injection, hemorrhages into the eyes, petechial hemorrhages and ecchymotic spots in the skin and mucous membranes, epistaxis, melena, hematemesis, hemoptysis, and gingival bleeding. No definite rash is ever noticed.

With the appearance of jaundice the pulse rate decreases. Pruritus is, as a rule, conspicuously absent. Herpes labialis is, as a rule, not found. There is no general lymphadenopathy.

Respiratory symptoms are present in about half of the cases. These patients have a cough, expectorate a great deal (rarely blood-tinged), have pharyngitis, bronchitis, and a patchy consolidation of the lungs. Most of

these cases are diagnosed as a viral pneumonia before the jaundice and characteristic urinary findings set in.

The cardiovascular system is usually affected during this stage. There is a tendency toward hypotension, and the blood pressure therefore is usually lower than normal. At times the heart actually becomes dilated, and hemic murmurs are not uncommon. Gallop rhythms, bradycardia, premature beats, auricular flutter and fibrillation, and pericardial friction rubs have all been described in Weil's disease. The electrocardiogram may show a prolonged QT and PR interval, defective AV conduction, functional or real incomplete AV block, low T waves, blocked auricular beats, sinus tachycardia, and a QRS complex which is low in voltage, is wide and slurred. It is a reversible type of heart disease, and in most cases the heart returns to normal during convalescence.

Central nervous system complaints include headache, delirium, apathy, hallucinations, disorientation, and restlessness. In the very severe cases the patient has a stiff neck with retraction of the head, a loss of consciousness and some of the other characteristic signs and symptoms of meningeal irritation.

*Nephritic or Uremic Stage.* Transition from the hepatic to the nephritic stage is not clear-cut. In fact, many authorities on the subject combine the hepatic and nephritic stages. During the septicemic stage there is a mild albuminuria, some diminution in urinary output, and an occasional red and white cell. During the hepatic stage, there is some degree of oliguria. In the urine there are found red and white blood cells and occasional casts. In this stage there is no retention of metabolites in the blood. At the onset of the uremic stage practically all patients have oliguria while a small percentage has anuria. In all fatal cases, anuria seems to be a constant finding. Albumin is present in large amounts in the urine, and there is glycosuria in about 10% of the cases. Red and white cells and granular casts are present in large numbers. There is a steady rise in blood pressure, a retention of nitrogen metabolites, and a definite decrease in kidney function as shown by the various kidney function tests.

*Convalescent Stage.* As the name implies, during this stage the patient is on his way to recovery. The jaundice begins to leave, and the uremic stage improves. More urine is secreted, the temperature returns to normal, and hemorrhages stop, but the patient still feels rather weak. Ordinarily convalescence is in the 3rd week, but it may not occur until the 5th to 6th week in certain cases. The last sign to disappear is jaundice which might persist for weeks. Relapses occur in about 20 to 25% of all cases, and this happens usually from the 3rd to the 5th week after the beginning of the disease.

**Laboratory Findings.** 1. *Hematologic Findings.* There is usually a microcytic hypochromic anemia present, the cells averaging 1.8 to 3.5 millions in number. Ashe<sup>3</sup> states that the platelets are normal in number and that the prothrombin time is normal. Most workers, however, agree with Senekjic,<sup>87</sup> who states that there is a slight reduction in the number of platelets, and that the prothrombin time shows moderate to marked prolongation. The bleeding and coagulation times are normal. The red blood cells do not show increased fragility. In fact, some authors state that the red blood cells show decreased fragility. The sedimentation rate is increased. As a rule, all authors report an active leukocytosis with an increase in polys and a shift to the left. Senekjic reports an active leuko-

cytosis of 10,000 to 30,000 in 83.4% of his cases. Six of his cases had a normal white blood count.

2. *Blood Chemistry.* There is a high and rising icteric index as the bilirubin blood level reaches 300 units and 90 mg. % respectively. The van den Berg reaction has been reported both as direct and indirect. Senekjic reports the van den Bergh reaction as being direct. Most authors disregard the van den Bergh reaction in this condition since it is not constant, and is of little diagnostic significance.

The chlorides, sugar, and cholesterol levels are normal. The urea and uric acid levels rise and reach their peak during the nephritic stage. Blood urea nitrogen levels of 50 to 100 mg. % are common, and Ashe reports some cases with blood levels of 150 mg. %. The serum proteins are slightly decreased. Late during the course of the disease the creatinine blood level rises. Senekjic mentions that a 10 mg. % creatinine level is a bad prognostic sign, while a level of 12 to 14 mg. % usually means that the patient will have a fatal outcome. The carbon dioxide combining power is normal or decreased. The hippuric acid test for liver function is somewhat reduced, and the cephalin-flocculation test is usually positive.

3. *Urinary Findings.* In all cases there is some degree of oliguria. In fatal cases there is complete anuria. Albumin, red and white cells, hyaline and granular casts, bile pigment and excess urobilinogen is present. Glycosuria is present in only a few cases. Kidney function tests show an impairment of kidney function.

4. *Spinal Fluid Findings.* These were mentioned before when leptospiral meningitis was discussed.

**Pathologic Findings.** During the septicemic stage, the spirochetes invade the internal organs such as the liver, adrenals, kidneys, muscles, prostate, thymus, appendix, testicles and epididymis. However, the early immunologic response in man leads to destruction of leptospiras in all the organs except the kidney and heart muscle where they can be demonstrated histologically.

*Liver.* There may be little or extensive change in the liver. In mild infections, there is merely biliary stasis, accumulation of leukocytes and lymphocytes in the portal spaces, cellular hyperplasia, and accumulation of hemosiderin. On the other hand, in severe infections, the destruction is seen grossly, with hypertrophy, loss of lobular markings and microscopically, coagulative necrosis, biliary stasis, fatty degeneration, marked macrophagic reaction, cellular reaction, and cellular infiltration; the hepatic cells are markedly altered, the normal cell structure absent and the sinusoids congested. The connective tissue reaction is never remarkable.

*Kidney.* Grossly, there is frequent hypertrophy, icteric coloration, variable hemorrhages and, in protracted infections, fibrosis. Microscopically, the lesions may be multiple; the tubular portion is most affected with necrosis and many casts. The glomeruli are often swollen and filled with exudate and bile precipitate; the capsular endothelium is proliferated. There may be fatty degeneration, cellular infiltration and edema of the interstitium. The proliferation of the connective tissue and fibrosis in protracted cases may be very severe. Hemorrhage may be so marked as to simulate hemorrhagic nephritis.

*Heart.* Occasionally, there is cardiac hypertrophy, often ecchymoses of the epicardium and endocardium. Microscopically there is subendocardial hemorrhage and round cell infiltration of the myocardium. In cardiac collapse, there is also vacuolar and granular degeneration of contractile fibers.



*Lungs.* Grossly, there is petechiation of the lungs and pleura. The parenchyma is edematous; the tracheal mucosa is ecchymotic. Bronchopneumonia is a frequent complication. There may be intraalveolar and intrabronchial hemorrhages, areas of leukocytic infiltration, and active phagocytosis.

*Intestines.* The changes are difficult to gauge due to a postmortem autolysis. Microscopically, there are discrete hemorrhages, edema, cellular infiltration, and evidence of degeneration of the muscle coats. Sometimes, the pancreas is the seat of inflammation and hemorrhage.

*Hematopoietic System.* Grossly, the lymph glands are hypertrophied and hemorrhagic. The spleen is hypertrophied in some cases. Microscopically, the lymph glands show cellular proliferation. The spleen shows evidence of homogenization, thickening of the reticulum, cellular proliferation, a macrophagic reaction with collection of hemosiderin. There is only feeble erythroblastic activity and little proliferation of white cells. Hematophagia is marked in all the organs and is characteristic of leptospirosis. Hematophagia, together with the feeble erythroblastic activity, explains the anemia.

*Nerve Tissue.* Little change is noted in the nerve tissue excepting for occasional scattering of hemorrhage and cellular infiltration.

*Eyes.* There are hemorrhages in the conjunctiva, occasionally, the deep layers, the choroid, retina, optic nerve, and even the orbit. The blood-vessels are dilated. There is occasional cellular infiltration and keratitis.

*Skin.* In the skin there are sometimes cutaneous and subcutaneous hemorrhages and perivascular cellular infiltration.

*Striated Muscles.* There is evidence of degeneration of muscle fibers, cellular infiltration and hemorrhage, these changes are most marked in the calf muscle.

*Suprarenals.* Early in the disease there is hemorrhage throughout the gland; later there is infarction. The parenchyma is infiltrated with round cells and leukocytes.

Summarizing this section, it is evident that the most severe pathologic lesions are in the kidney. When the liver is markedly affected, the combination (together with the changes in the kidney parenchyma) may be termed the hepatorenal syndrome. This syndrome is characterized by abundant karyokinesis in the liver and kidney cells and especially by the extensive hematophagic reaction.

*Diagnosis.* The diagnosis of Weil's disease is made by a careful study of the clinical findings and by means of certain laboratory procedures. As in typhoid fever, the procedures necessary to establish the diagnosis of Weil's disease vary, depending upon the duration of symptoms.

A presumptive diagnosis can be readily made in a majority of cases presenting (1) the classical symptoms of sudden onset of chills, headache, fever, arthralgia, myalgia, injection of the conjunctivæ, the hemorrhagic phenomena, and leukocytosis. (2) Hepatomegaly, and jaundice on the 5th to 7th day of the illness. However, anicteric cases must be considered. (3) Albuminuria, casts, and evidences of kidney failure with retention of metabolites in the blood. (4) A definite history of exposure. However, the final proof that the patient has Weil's disease must come from finding the causative organism in one way or another. It is because of the protean nature of the disease that all clinical diagnoses must be proved by the laboratory methods of diagnosis.

Accurate diagnosis is made in the laboratory and depends upon: (1) detecting leptospiras in fresh blood, (2) by culture from the blood, (3) by

inoculation of the blood into a suitable laboratory animal, (4) detection of the organism in the urine and the inoculation of laboratory animals with it, (5) serologic examination, (6) Fontana and Levaditi stains of tissues, and (7) muscle biopsy.

Before a discussion of these various laboratory procedures is made, it might be well to mention a statement from an article by Reid and Holt.<sup>82</sup> They say that emphasis should be placed on the fact that no single laboratory examination has proven entirely satisfactory for the diagnosis of Weil's disease because of some fallacies in each test.

1. *Dark-field Examination.* During the septicemic and hepatic stages, a dark-field examination of the patient's blood is the best method of diagnosis. Strong<sup>95</sup> emphasizes that in every suspected case, a search should be made with the dark-field illumination for the leptospira. He also mentions that thick films may also be stained by Giemsa's solution for examination. The technique consists of examining blood under dark-field illumination with either the usual high dry lens or the oil-immersion lens of the average microscope. *L. icterohæmorrhagiæ* appears as actively motile spirochetes. The characteristics of the organism have been described in the early part of this paper. The only difficulty one encounters in identifying the organism is the presence of myriads of minute particles of fibrin and other partially precipitated protein normally seen in blood which are in constant Brownian motion. Schultz<sup>86</sup> observed parts of degenerated red cells and pieces of fibrin which resembled *L. icterohæmorrhagiæ*; he called these pseudospirochetes and emphasized the importance of having an experienced pathologist confirm all suspicious findings. Fortunately for diagnostic purposes, Ashe<sup>3</sup> says that when *L. icterohæmorrhagiæ* is present in the blood, it is usually present in large numbers. Also, that incubation at 27° C. (in the vest pocket) will frequently increase the number of organisms in the specimen and facilitate demonstration. Strong,<sup>95</sup> on the other hand, says that the organisms are rarely numerous and are only present during the first days of illness, so that they are frequently not detected. Better results have been obtained by centrifuging fresh citrated blood, but Schüffner<sup>85</sup> has emphasized the difficulty of precipitating the spirochetes even at high speeds. Some workers advocate triple centrifugation. Of Senekjic's<sup>87</sup> cases, 23% were diagnosed by dark-field examination.

In the 2nd week of the disease the spirochete may be occasionally found on direct dark-field examination of the cerebrospinal fluid. Because not infrequently there are spirochetes of many varieties in normal urine, direct dark-field examination of urine is not satisfactory.

2. *Animal Inoculation.* For therapeutic reasons, it is most desirable to demonstrate the organism directly in the blood stream in the 1st week of the disease, because it is during this period that specific therapy is most valuable. In the early part of the disease, blood from the patient is used; in the later days of the disease, it is better to use the urine.

•For this procedure, it is necessary to choose the proper laboratory animal. Now any animal will do. The most common animal used is the guinea pig, one weighing 175 gm. or less. Unfortunately, not all guinea pigs will die when inoculated. They must be young. Das Gupta<sup>15</sup> showed that young guinea pigs born of mothers actively immune to leptospiral infection exhibit marked resistance against homologous infection. This resistance persists until the 62nd day after birth, but not up to the 188th day. He suggests that the female guinea pigs which have acquired immunity by some means or other should not be used for breeding pur-

poses, as the young borne of these animals are unsuitable for diagnostic inoculations. Morton<sup>72</sup> prefers to use white mice or Syrian hamsters. Young white mice are very susceptible to *L. icterohæmorrhagiæ*. The death rate in inoculated animals is approximately 100% in 3 week old mice, but this high mortality rate falls off rapidly if older mice are used. Although Morton limited his work to 1 strain each of the 2 species of leptospira, it appears that Syrian hamsters may be useful as laboratory animals in work with *L. canicola* and *L. icterohæmorrhagiæ*. Reid and Holt<sup>82</sup> (after Packehanian) suggest the use of certain species of deer mice as suitable susceptible small laboratory animals for experimental studies of icterohemorrhagic spirochetosis, and for the diagnosis of Weil's disease.

In some instances, leptospiras have been detected in the blood as late as the 8th and 10th day. When not found in the blood, 3 to 5 cc. of it or of centrifuged plasma should be inoculated into the peritoneal cavity of the guinea pig. The animal usually dies in 10 to 12 days, with characteristic pathologic lesions. Schüffner<sup>85</sup> states that the leptospiras can frequently be detected in drops of fluid from the peritoneal cavity of the animal after several days, usually being present by the 3rd. The organisms can be demonstrated in the liver, the lung, and the kidney of the animals, either by section and staining with the Levaditi or Giemsa stains, or directly by dark-field examination of an emulsion of these organs. Rathbun and Waghelstein<sup>79</sup> realize that different strains of the organism vary in virulence. They recommend that if the inoculated guinea pig does not die by the 12th day, it should be killed, and that further guinea pigs should be inoculated with the blood, liver, and kidney of the initially inoculated animals. Three such passages should be carried out before a negative report is made. Exact identification of the strain of spirochete must, of course, be done serologically.

After the 1st week of the disease, leptospiras should be searched for in the urine. They are usually most prevalent from the 10th to the 20th day of the disease. Centrifuged sediment of fresh urine should be examined directly at first, and then guinea pigs should be inoculated with it. This latter method has proven unsatisfactory in many hands, and is probably one of the very important reasons for failure to establish the diagnosis in this country. In order to assure good results, Ashe<sup>3</sup> gives the following precautions: (1) The urine must have stood not more than an hour before the inoculation is made. (2) Strongly acid or strongly alkaline urine quickly destroys *L. icterohæmorrhagiæ*, and the patient must be given some agent to make his urine approximately neutral when voided. (3) The guinea pig must be young (175 gm. or less).

3. *Agglutination Reactions.* In the 3rd and subsequent weeks of the disease, *L. icterohæmorrhagiæ* produces in the host very specific agglutinins which can be measured.<sup>67,85</sup> These are among the most specific antibody reactions known. Schüffner<sup>85</sup> believes agglutination tests are best carried out with leptospira cultures preserved in 5% formalin, as they do not lyse so readily as the living organisms, and he has found that the killed leptospiras agglutinate up to the highest dilutions compatible with the strength of the serum. If living leptospiras are used, agglutination appears only in the lower dilutions, as in the higher ones lysis sets in, rendering agglutination impossible. However, sometimes the formalized organisms are often rendered unsatisfactory for the test after some weeks, since the leptospiras usually become matted together into feltlike clots.

In the average case, according to Ashe,<sup>3</sup> after 3 or 4 weeks the blood serum of the patient will agglutinate avirulent culture of *L. icterohæmor-*

*rhagiæ* in dilutions of 1:10,000 to 1:300,000, and will not agglutinate any other known strains in a titer above 1:250. This agglutination reaction is useless before the 9th or 10th day of the disease, because no specific antibodies are found. When found in high titer after the 14th day, it is diagnostic. Senekjie warns of the possibility of one being misled by an amnestic reaction in a patient, but serial agglutination tests showing a rapidly increasing titer serves as an accurate diagnostic test. Tiffany,<sup>97</sup> in discussing the agglutination test for Weil's disease, says that a titer of 1:1000 indicates a present or recent infection, but when found by an experienced technician, any titer, however low, merits investigation. Packchianian and Tom,<sup>78</sup> in reporting their cases, found the average level of agglutination titer during the active phase of the disease to average 1:23,000. Most observers now agree that the agglutination in dilutions of 1:300 or above is diagnostic. Senekjie<sup>87</sup> reports that 24 of his cases, or 80 %, were diagnosed by means of the agglutination reaction. He found the titer of antibodies to be rising during the hepatic stage, reaching the diagnostic level at the nephritic stage. The peak was reached during convalescence. A summary of the agglutination titers found by Senekjie in these cases is as follows:

No. of cases	Agglutination titers
10 . . . . .	1:300-1:1000
3 . . . . .	1-3000
3 . . . . .	1-10,000
1 . . . . .	1-30,000
2 . . . . .	1-100,000
5 . . . . .	1-1,000,000

All workers in the subject agree that strong false positives are non-existent. A negative reaction after the 30th day of illness rules out Weil's disease.

There are three main types of agglutination tests: (1) the microscopic, (2) the macroscopic, and (3) the agglutination absorption test. Brown and Broom<sup>8</sup> think that the macroscopic test is not nearly as sensitive as the microscopic, and that in certain serums of low titer, such as those shortly after the 6th day of the disease, the reaction may not appear if the macroscopic test only is employed. Starbuck and Ward,<sup>91</sup> in February, 1942, made a comparative study of the results obtained with a newly developed macroscopic agglutination test and the standard microscopic agglutination test against *L. icterohæmorrhagiæ* on 356 human serums and 10 immune rabbit serums. They concluded that the macroscopic agglutination test against *L. icterohæmorrhagiæ* is specific and sufficiently sensitive to be of value in the diagnosis of acute cases of leptospirosis. They mention, however, that in an epidemiologic survey, that the standard microscopic test would probably be preferable since former cases of leptospirosis or inapparent infections might not be detected by the macroscopic method. Brown<sup>9</sup> describes a rocking-slide test, a type of macroscopic agglutination test. The test essentially consists in rocking to and fro on a slide for 10 minutes small quantities of varying dilutions of the patients' serum in the presence of a heavy suspension of *L. icterohæmorrhagiæ*; this saline suspension is formalized to a concentration of 0.2 %. The dilutions of the serum are made in the depressions of a painter's palette. They are then mixed with an equal volume of antigen and placed on a slide just over the depressions in the palette. This is made to rock for 10 minutes, and the result is read by means of a hand lens against a dark background. The results of this method and the plain macroscopic have been con-

sistently identical, but in every instance Schüffner's microscopic technique has given a titer three times higher than that obtained by either of the other methods. However, the rocking-slide method, given a suitable antigen, will produce a result within 15 minutes of the receipt of the serum, and that it is reliable enough to justify the administration of serum.

Schüffner<sup>85</sup> and others merely used the agglutination absorption test to differentiate various strains of leptospiras. Senekjic mentions Lederle's slide agglutination antigen for the quick diagnosis of the disease, but he says that it requires checking with the regular agglutination technique.

4. *Complement Fixation Test.* Ashe<sup>3</sup> mentions that complement fixation reactions have been described but are less simple of interpretation, and he recommends the agglutination test as diagnostic. Kramer<sup>50</sup> merely mentions that the complement fixation test is helpful, but does not evaluate it.

5. *Culture.* Some workers believe that the diagnosis is most easily made from cultivation, in the incubator, by direct inoculation of the blood into blood agar. Schüffner<sup>85</sup> also recommends culture as a desirable method of diagnosis. By using this method, he cultivated the organism from 51 cases, of which 18 were without jaundice.

6. *Muscle Biopsy.* This does not seem to be very practical, although Blake<sup>6</sup> recommends biopsy of the gastrocnemius muscle when the diagnosis is otherwise doubtful. Vacuolation, swelling, loss of striations and hyalinization of isolated or groups of adjacent muscle fibers and infiltration with histocytes, neutrophils, and plasma cells may be seen on microscopic examination.

7. *Levaditi, Fontana and Giemsa Stains.* When examining fluids, Fontana's stain is used. Levaditi's stain is used on tissues. These staining techniques are used chiefly in finding the organism in the tissues and fluids of a person who died of a disease suspected to be Weil's disease. More often, however, these stains are used to demonstrate the organism in the liver, lung, and the kidney of the experimental animal after inoculation in order to diagnose the disease.

**Differential Diagnosis.** Before discussing the diseases with which Weil's disease may be confused, it might be well to mention some of the more atypical forms of this disease as taken from various sources in the literature.

1. Malaria-like onset: fever lasting for 24 to 48 hours only; late albuminuria; hemorrhages during afebrile period.

2. Complete absence of pains: slight fever with prostration; albuminuria and jaundice. Very few cases of this type were reported.

3. The pneumonic or influenzal type with massive consolidation of one or both lungs. This type was reported rather frequently.

4. The "melena" type with fever and profuse hemorrhage.

5. The cerebral or meningeal type with early unconsciousness, and delirium.

6. The cardiac or nephritic type simulating acute congestive cardiac failure.

7. Intensely jaundiced type with "black vomit."

8. The "yellow fever" type with "black vomit."

9. The non-icteric type. The cases are generally mild. Many authors report about one-half of their cases being of this type.

10. Chronic meningeal and a chronic icteric form were encountered in about 10% of the reported cases.

There are quite a few diseases with which Weil's disease may be confused. I will discuss the differential diagnosis of the more common ones in detail.

*Typhoid Fever.* This is commonly diagnosed because in many cases the pulse may be relatively slow for the height of the fever. The absence of rose spots, the negative blood culture, the marked calf tenderness, and cells in the spinal fluid, will usually rule out typhoid. The incubation period of typhoid is usually about 2 weeks, and for Weil's disease it averages about 9 days.

*Influenza.* In mild cases in which no jaundice develops, many cases have gone, and will go, undiagnosed as anything but "la grippe." The chief aid seems to be that in influenza-like states the patient promptly feels better when the temperature drops; in Weil's disease the patient feels quite badly for several days after the temperature becomes normal. Vomiting is much worse and much more frequent than in influenza, and a careful study of the urine and blood may show minimal evidence of renal and hepatic disease which would otherwise be overlooked.

*Septicemia.* Weil's disease may be confused with septicemia in which jaundice is a symptom. Helpful in differential diagnosis are the presence of intense muscle pain and tenderness in the former and a positive blood culture in the latter. Sometimes the jaundiced patient who has septicemia does not have choline.

*Acute Catarrhal Jaundice.* Ordinarily patients with this disease have very few complaints. Lassitude, anorexia, slight abdominal distress, nausea, and occasional vomiting comprise the subjective manifestations. Often patients do not seek medical attention until their scleræ are observed to be yellow.

On the other hand, patients with leptospirosis usually become ill suddenly with a prostrating malady which closely resembles severe influenza, and seek medical attention before jaundice sets in. Icterus becomes deeper more rapidly in Weil's disease than in acute hepatitis. Severe muscular pain and tenderness, especially of the back and calf muscles, should lead to the suspicion of the existence of leptospirosis. If conjunctivitis and hemorrhagic and meningitic manifestations are present, the suspicion is strengthened. In acute catarrhal jaundice, the white count is relatively low and lymphadenopathy and a palpable spleen are the rule. The reverse is true in Weil's disease. Evidence of renal disease, meningeal involvement, and a hemorrhagic tendency are absent in catarrhal jaundice. In Weil's disease, the time of onset of the jaundice, 3 to 9 days after the beginning of severe symptoms, should lead one to search for the etiologic spirochete.

*Yellow Fever.* In severe cases in some parts of the world, the chief differential diagnostic problem is presented by yellow fever. In this country the problem should rarely arise. It is of interest that Noguchi<sup>76</sup> was led to believe that a spirochete was the cause of yellow fever, because he examined the blood of patients with Weil's disease in the erroneous belief that they had yellow fever. Geographic limitations on the occurrence of yellow fever will often rule out this disease. The course of the temperature is somewhat different in the two diseases. In yellow fever, after 2 or 3 days, there occurs a remission lasting from 3 to 48 hours, which is followed by a relapse during which a marked relative bradycardia is present (Faget's sign). Otherwise the symptoms are the same, as in the initial period of fever. The second febrile period lasts from 2 to 5 days.

Probably of greatest value in the differential diagnosis is the white blood cell count, for leukopenia is the rule in yellow fever. Albuminuria occurs in both diseases, but appears earlier in yellow fever and becomes more

severe each day. Inasmuch as death or recovery will have taken place before the results of mouse inoculation and protection tests are available, these procedures have little practical value.

Ashe<sup>3</sup> states that the characteristic intense facial flush and very red lips of yellow fever are not present in Weil's disease, and that the face of the patient shows anxiety instead of lethargy.

*Relapsing Fever.* The clinical differentiation between leptospirosis and relapsing fever also is very difficult. Fever, icterus, hemorrhage, muscle pain, and signs of meningitis are common in both diseases. The first febrile period in relapsing fever, and the first stage of Weil's disease, both last about 6 days; relapses occur in both diseases during the 3rd week. The spleen and liver are said to be enlarged in relapsing fever, whereas the former is rarely, and the latter is not usually, enlarged in leptospirosis. Leukocytosis is present in both diseases. The diagnosis of relapsing fever is based on finding large spirochetes in stained films of blood taken during relapses.

*Acute Yellow Atrophy.* This should be differentiated rather easily, because it usually begins as a mild disease with symptoms similar to those described as occurring in "acute infectious jaundice." The patient with acute yellow atrophy becomes worse at a time, after 2 or 3 weeks, when the patient with leptospirosis is recovering. A diminution in the extent of liver dullness and the presence of leucine and tyrosine crystals in the urine are of diagnostic aid.

Other possible confusing diseases of minor importance, as far as differential diagnosis is concerned, are syphilis of the liver, liver abscess, and blackwater fever.

**Prophylaxis and Control.** Wani<sup>106</sup> in 1933 prepared a vaccine by treating emulsions of injected liver or cultures with 0.5 % phenol and refrigerating for 7 days. Twelve hundred and sixty-two miners were inoculated who showed a morbidity of 0.3 %, while in the control non-vaccinated group the morbidity rate was 1.12 %. The serums of such persons protected guinea pigs against lethal doses of leptospiras. Das Gupta<sup>15</sup> in 1942 also reported active immunity in man following injection of leptospira vaccine. In 1938, van Theil<sup>102</sup> used living avirulent strains of leptospira which were maintained in cultures for 8 years. He inoculated 5 persons with this strain. Four developed atypical attacks, but the fifth manifested icterus. He points out that this case proves that the injection of avirulent strains of leptospiras are not entirely without danger, and especially on account of the greater susceptibility of some individuals. According to Walch-Sorgdrager,<sup>105</sup> immunization with vaccines containing killed leptospiras has been used on a large scale in Japan by various workers with apparently some success. In addition, Alicata<sup>1</sup> has successfully immunized dogs against leptospirosis by the use of 0.2 % formalized leptospira antigen. Senekjic mentions that it is not advisable to use living leptospiras, since we do not know the factors which enhance the virulence of the organism. He further states that, since the disease is only sporadic in the United States, there is no need for prophylactic inoculation here.

The prevention of the disease rests largely on the following measures:

1. Control of rats; these animals should be especially prevented from entering establishments where the floors are kept wet, such as basement shower-rooms.
2. Protection of feet by the use of boots or shoes whenever working in wet areas frequented by rats or dogs.

3. Avoidance of swimming or wading in fresh water streams or ponds and avoidance of drinking from irrigation ditches frequented by rats.

4. Proper veterinary care of sick dogs and cats; these animals should not be fondled, and contact with their urine should be especially avoided.

5. Active immunization of individuals in localities where exposure to infection exists, if such a measure be possible.

6. As the infection appears to be transmitted through the medium of the urine and feces, sterilization of these discharges from those sick with the disease should be practiced. Hoagland, Harris and Chinen<sup>42</sup> in 1943 state that when a patient with Weil's disease is being treated, the usual contagious disease precautions should be taken by the ward personnel. The patient should be isolated and should wash his hands with 1 % cresol solution after each urination. The urine should be disinfected before it is disposed of. They also suggest that it may be possible to end the urinary carrier state by giving mandelic acid and urine acidifying drugs.

7. Scrupulous care to prevent food from being contaminated by the discharges of rats and mice also is of great importance.

8. Fish workers, sewer workers, and workers in damp mines, should take care to prevent or protect abrasions of the skin which favor infections.

9. Since fish remnants especially attract rats, and since the spirochetes live in the slimy water, care should be taken to remove all offal at the end of each day's work. The floors, benches and tables of fish warehouses should be vigorously hosed with water and thereafter treated with a suitable disinfectant. One worker has found a hyperchlorite solution in a dilution of 1:4000 has a lethal effect on leptospiras.

10. Laboratory workers must take precautions in handling infected animals and wear gloves.

**Treatment.** Soon after the cause of Weil's disease was established, a search for protective antibodies in convalescent patients was begun. The Japanese, thanks to the work of Inada,<sup>44</sup> were the first to demonstrate such antibodies and to use these agents in therapy. By 1916, both horse serum and goat serum containing antibodies against *L. icterohæmorrhagiæ* had been produced. A few years later, a curative rabbit serum was developed. The most widely used sera came from horses whose blood has been raised to an agglutinating titer of 1:100,000 or higher against *L. icterohæmorrhagiæ* and *L. canicola*. Inada<sup>43</sup> fixes the dose at approximately 60 cc. of such serum. Walch-Sorgdrager,<sup>105</sup> Griffith,<sup>35</sup> and Inada indicate that this form of therapy is effective in lowering the mortality rate, especially if given in the first 6 days of the disease. These represent reports from Holland, England, and Japan. Comparable favorable reports have also come from France and Germany. In Japan alone, Inada reports that the mortality rate in one group of cases was lowered from 30.6 to 18.3 %. Strong<sup>95</sup> recommends that the serum be given intravenously at intervals of several hours for at least 3 or 4 days. Twenty cc. at least should be used for each injection. Tokuyama<sup>99</sup> in 1939 studied 9 patients in Hawaii, 6 of whom were treated by intravenous injections of immune serum. Four patients recovered and 2 died. Of the 3 untreated patients, 2 died. There was little evidence that the treatment had any effect, although in 2 instances the infection was followed by general improvement. Schüffner<sup>85</sup> points out that if the serum is not given until jaundice appears, its efficacy is very greatly reduced. D'Silva<sup>21</sup> in 1942 tried antileptospira serum in 10 cases and his results were very disappointing. He gave doses of from 40 to 60 cc. intravenously. The failures might have been due to the difficulty in obtaining a polyvalent and potent antiserum against the



different local stains of leptospira. Ashe<sup>3</sup> concludes from his studies that the treatment of choice is immune serum. As yet, the American drug houses have done nothing about preparing such sera, nor can they be expected to do so until city and state laboratories make available the necessary diagnostic procedures, and until the true incidence of the disease in the United States becomes known.

Larson<sup>55</sup> in 1943 showed that serum from patients convalescent from Weil's disease and immune rabbit serum and plasma prevented the death of young white mice infected with *L. icterohæmorrhagiæ*. He also showed that the effect of these materials is marked if administered on or before the 4th day after injection. Ashe<sup>3</sup> in 1941 reported the first serum treated case in this country. He gave 500 cc. of whole blood from a person who was convalescing from Weil's disease to a patient who had the active disease. The blood was given on the 9th day of the disease, at which time the patient had been completely anuric for a period of 30 hours. Within 6 hours after therapy he began to void, and improved steadily thereafter. No antibodies were found in the patient's serum before therapy, but they were abundant thereafter. Gaines<sup>29</sup> gave 30 cc. (a small amount) of convalescent blood intramuscularly to 1 patient, but complete identification of the infecting spirochete was not made in the recipient. Walch-Sorgdrager<sup>105</sup> show that, while the severity of symptoms and the mortality are favorably affected by the use of immune serum, the duration of the febrile period is not altered. When serum has not been effective, it is felt by many that an adequate dose was not given. Clapper and Meyers<sup>12</sup> in 1943 report that these immunotransfusions may be of value in treatment and a more extended trial in their use is certainly justified. Ashe mentions that, until immune sera appear on the American market, convalescent serum or whole blood transfusions should be used when possible.

Soon after the recognition of *L. icterohæmorrhagiæ* as the etiologic agent in Weil's disease, many attempts were made to kill the spirochete *in vivo* with specific arsenicals such as salvarsan and neoarsphenamine, but without success. Furthermore, there is a real danger in administering certain toxic substances in the presence of much liver and kidney disease. Neoarsphenamine has been used by some workers with reports of fairly good results.

Sazerac and Nakamura<sup>84</sup> in 1927 used soluble bismuth preparations, such as sodium bismuth tartrate given intravenously, and have shown it to be effective and non-toxic in guinea pigs. In Germany, a few human cases have been treated with soluble and colloidal bismuth compounds with reported success. There is still dispute as to whether the bismuth is bactericidal or bacteriostatic, or whether it merely stimulates the normal body defense mechanism. Uhlenhuth and Seiffert<sup>101</sup> in 1929 used soluble colloidal bismuth yatrien compound and reported good results. Antimony compounds have proven useless.

Because certain soaps and resins are known to dissolve the spirochete *in vitro*, sodium ricinoleate has been used experimentally in animals with some beneficial results, but there are no reports in the literature that these agents were ever useful in man.

Ashe<sup>3</sup> reports the use of sulfanilamide as useless. He treated one of his cases with large doses of sulfanilamide (10 gm. daily for 3 days) during the bacteremic first stage, and it did not alter the number of organisms in the blood stream; nor did it in any way influence the course of the disease. Walch-Sorgdrager<sup>105</sup> used prontosil in the Netherlands without benefit.

Senekjic<sup>87</sup> also reports that he used the sulfa drugs without any apparent effect. It was only good to help combat secondary infections.

Since hyperimmune horse serum and convalescent serum are not available and since the diagnosis is usually made late during the course of an infection, it is obvious that specific treatment is not practical. The treatment is, therefore, chiefly symptomatic. The basic principles should be: ensuring rest, quickly eliminating the toxins, and "anticipatory therapy," *i. e.*, preventing the onset of the grave symptoms and sequelæ, such as hemorrhages, cardiac failure, toxemia, cholemia, anuria, persistent hiccough and vomiting, hyperpyrexia, parotitis and cystitis. A brief of the accepted supportive treatment is:

1. *Rest.* Absolute rest in bed is essential in view of the possibility of sudden heart failure due to cardiac musculature being involved during the acute and convalescent stages.

2. *Sedation.* Early administration of sedatives was found necessary owing to the intensity of muscular pains and restlessness.

3. *Elimination.* Elimination of toxins by diuretics and diaphoretics and by purgation. D'Silva<sup>21</sup> recommends the use of camphor as a diaphoretic. He also advises the use of urotropine since it acts primarily as a biliary and urinary antiseptic and secondarily perhaps as a spirocheticide against the leptospiras, which are believed to lodge inside such organs as the liver, gall bladder and kidneys. Moreover, urotropin, being excreted by the meninges, proved a valuable remedy in the meningeal type of the disease. It also prevented subsequent bacilluria and parotitis. "Cata-gone" by intravenous injection was tried with great success in 10 cases in place of urotropin.

4. High carbohydrate, protein, vitamin diet to support the liver. White and Prevost<sup>108</sup> advise the use of liver extract along with the usual supportive measures.

5. Calcium gluconate given parenterally.

6. *Fluids* must be adequate. They may be administered by mouth, hypodermoclysis, or by intravenous infusion. Saline and glucose infusions should be given frequently.

7. Small *transfusions* are helpful in many cases.

8. If kidney failure starts to occur, increase the amount of *glucose* being given, give caffeine derivatives in moderately large doses, use diathermy and hot packs over the kidney regions. Mercurial diuretics are contraindicated.

9. Cardiac stimulants are indicated when there is derangement of cardiac function.

10. During convalescence, various tonics, vitamins and iron should be given.

**Prognosis.** According to Ashe,<sup>3</sup> the prognosis is dependent upon the following factors: (1) age of the patient; (2) the presence or absence of jaundice; (3) the degree of renal failure; (4) the function of the heart; (5) the extent of the hemorrhagic diathesis.

Weil's disease is practically unknown in infants, and is rare in children. The mortality rate increases rapidly with advancing age. According to Walch-Sorgdrager,<sup>105</sup> in the fatal cases, death usually occurs between the 9th and the 16th day. Inada<sup>44</sup> reports the Japanese fatality rate in untreated cases as being 30%. Strong<sup>95</sup> mentions that the mortality rate has varied in different countries from 4 to 32% in Europe to 48% in certain Japanese outbreaks. The virulence of the outbreak has varied in different countries, and a varying susceptibility in individuals has been demon-

strated. In larger series of cases in Europe, the mortality rate ranges from 11.9% (some of these were apparently serum-treated) to 60% in the most severe epidemics. In the United States, the mortality rate<sup>3</sup> to date is about 30%. Senekjic<sup>87</sup> in 1944 reports a mortality rate of 16.6% in his cases. The mortality in the Andaman Islands has been reported as 18.7% and in the Isle of Syra (Greece) as 12%. In the sugar cane cutters of Queensland, a morbidity of 18% and a mortality of about 4% was reported.

Walch-Sorgdrager reported the following series from Holland:

	Died	Fatality rate %
Out of 11 persons aged 1 to 10 . . . . .	0	0
Out of 210 persons aged 10 to 40 . . . . .	15	7.1
Out of 49 persons aged 40 to 60 . . . . .	12	24.0
Out of 15 persons aged 60 or over . . . . .	9	60.0
Out of 85 persons of unknown age . . . . .	8	9.4
Totals, 370 cases . . . . .	44	11.9

Of the 370 cases, approximately 50% were jaundiced. The number of serum treated cases is not stated. Schüffner<sup>88</sup> in 1934, also reporting cases from Holland, found 452 cases in 10 years, among whom there were 46 deaths, or 10.2%. In his cases with jaundice, from 1924 to 1931, a mortality of 32% occurred, and in 1932 to 1933 a mortality of 16%. He thought that the lower mortality in the later years was due to the lessened virulence of the disease and in part to the effects of serum therapy, the use of which has been considerably extended in Holland. Schüffner believes no one dies of Weil's disease unless suffering from jaundice, and that Weil's disease without jaundice is as harmless as any other leptospirosis which never shows jaundice in its course, like "swamp fever," or "seven-day fever." Walch-Sorgdrager is the only worker to report a death which occurred without jaundice. He reports one instance of this nature. The intensity of the jaundice when present is probably not nearly as significant as the patient's age, although icteric indices of over 200 should always be looked upon gravely.

In the typhoidal, uremic, and meningeal forms, the prognosis is usually bad. It is especially grave when the cerebrospinal fluid is under pressure and contains an excess of albumin and leptospiras in large numbers. Nevertheless, death does not always occur. Murgatroyd<sup>74</sup> in 1939 reported a recovery from a case of meningitis in which the leptospiras were recovered from the cerebrospinal fluid months after the onset of the disease.

The degree of renal failure as indicated by the urine output and the degree of urea retention, is important for prognosis. Oliguria and a high blood urea are usually serious, and anuria is always a grave sign. A high blood urea without oliguria is usually not a serious sign.

In most cases, the cardiovascular system responds well to the disease; but occasionally a very rapid pulse, out of proportion to the temperature and associated with a relatively low blood pressure, is encountered. Pronounced and long-continued bradycardia is of serious significance.

Usually, the hemorrhagic diathesis is not of significance, but rarely, in the very ill older individuals, bleeding from the respiratory, gastro-intestinal, and urinary tracts may become so serious as to become a definite hazard to life.

In Japan, it has been definitely shown that early diagnosis and therapy can materially lower the mortality rate in all groups.

**Complications.** Many complications may occur during and soon after the course of the disease. Perhaps the two most common complications are iridocyclitis and optic neuritis. Reports of iridocyclitis are fairly common in the German literature, and one worker observed it in 44 % of his cases including the mild ones. In the Netherlands the figure is given as 10 % and is considered a minimum.<sup>105</sup> Walch-Sorgdrager could find no cases without recovery. Optic neuritis is apparently less common, and is not of much importance. Rathbun and Waghelstein<sup>78</sup> mention that iritis or iridocyclitis is present in from 10 to 44 % of patients. Other complications reported by these men are meningitis with complete paralysis and skin eruptions which occur in 10 to 36 % of patients.

St. Amant<sup>90</sup> in 1943 mentions certain nervous complications that may occur during the course of the disease:

1. Cerebral symptoms, such as headache, restlessness, dizziness, and bradyphrenia, due to the general infection are very common.
2. True meningitis with changes in the spinal fluid and occasionally with spirochetes in the spinal fluid is also fairly common. Meningitis may be the only manifestation of Weil's disease.
3. Symptoms indicating an affection of the nerve parenchyma, which in milder cases (reduced or abolished tendon reflexes, possibly slight paresis) may conceivably result directly from the meningitis as a spread to the nerve parenchyma.
4. In rare cases, complications indicate a more severe affection of the cerebral parenchyma which is not due to a spread from meningitis but is a complication *per se*. It is probable that the spirochetes may tend to attack the nerve parenchyma, in view of the fact that complications involving the peripheral nerves are not uncommon.

A few rare complications have been described, which may be fatal: such as myocarditis, acute vegetative endocarditis in which leprospiras are found, parotitis, and terminal purulent meningitis. Inada<sup>44</sup> reports a case where the fatal complication was a purulent meningitis. Severe hemorrhages and multiple liver abscesses are also rare complications of Weil's disease.

**Summary.** A brief review of Weil's disease as it occurs in foreign countries is presented with a more detailed review of the disease as it exists in America and Great Britain, placing special emphasis on the more recent findings and reports.

Judging from the American literature, Weil's disease is probably not rare in this country; and since, untreated, it has a mortality rate of about 30 % in jaundiced cases, there is every justification in calling attention to this 54 year old disease. The physician should be alert to confirm or to exclude the diagnosis of leptospirosis on encountering an acute febrile illness even in patients without jaundice, in one whose work is likely to involve exposure to rat-contaminated surfaces, particularly if the illness resembles influenza, pneumonia, or enteric fever, or if renal insufficiency or a hemorrhagic tendency is present. Physicians should realize that leptospirosis is a protean infectious disease with symptoms sometimes so mild that diagnosis is difficult except by bacteriologic means. The more frequent recognition and diagnosis of Weil's disease would appear to depend on a wider appreciation of its prevalence, a greater familiarity with its clinical symptomatology, particularly that of the initial pre-icteric stage, and a more frequent use of laboratory tests of proved diagnostic value at appropriate stages of the infection. Many authors advise making Weil's disease a reportable

infection here in the United States, because the condition seems to be more prevalent than the reported figures would indicate.

A general recognition of the disease in the United States is desirable, because therapy is simple and effective. Until the true incidence and importance of the disease is realized by American physicians, the much-to-be-desired goal will not be obtained.

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## NEUROLOGY AND PSYCHIATRY

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## RELATIONSHIP AND FUNCTION OF THE PYRAMIDAL TRACT

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THE prevalent teaching regarding the voluntary motor system is summarized by Tilney and Riley<sup>50</sup> (1938). "The impulses of this volitional control arise in a certain area of the cerebral cortex known as the Rolandic or motor area. This portion of the brain contains many large pyramidal

\* Now on active service.

cells whose axones, the pyramidal fibers, eventually bring the impulses of volitional control to the motor cells of the ventral gray column. There is also a type of cortical control which exerts an inhibitory influence upon the tone of the muscles. . . . When the connection between cortex and ventral horn cells is interrupted, the patient not only loses the power of volitional control of the affected muscles but the muscles themselves become unusually contracted. . . . Such hypertonicity or spasticity is accompanied by an increase in reflexes of the affected part."

The following assumptions have been made regarding the pyramidal or corticospinal tract: (1) It originates in the giant Betz cells of the motor area (area gigantopyramidalis, Area 4 of Brodmann, Area FB of Economo and Koskinas). (2) It terminates in synapses with anterior horn cells. (3) It is the upper motor neuron and is the anatomic substratum for all voluntary movement. (4) It is not only responsible for movement but is also an inhibitory mechanism, exercising control over the lower motor neuron. A lesion of the pyramidal tract therefore gives rise to (a) spastic paralysis, (b) hyperactive reflexes and (c) pathologic reflexes.

A large body of experimental evidence is now available which casts considerable doubt upon these assumptions.

**Origin.** In 1874 Betz,<sup>3</sup> a Russian histologist, described the giant pyramidal cells in the fifth layer of the precentral cortex. The idea that the pyramidal tract has its origin in these giant cells has been impressed upon neurologic literature largely as a result of 3 investigations conducted in England during the early portion of this century. These investigations were the electrical stimulation experiments of Grünbaum and Sherrington<sup>25</sup> (1903) on the cortex of the higher apes, the cytoarchitectural descriptions of Campbell<sup>6</sup> (1905), and the studies of retrograde degeneration following spinal cord lesions by Holmes and Page May<sup>29</sup> (1909). Campbell, following the early experiments of Grünbaum and Sherrington on the motor area of higher apes, concluded that the Betz cells represented the true motor elements of the cortex. He believed that the area of Betz cell distribution (his "precentral area") coincided exactly with the motor area as delimited by Grünbaum and Sherrington. It was only after the publication of Campbell's work that Leyton (Grünbaum) and Sherrington's final study appeared<sup>36</sup> (1916), enlarging their original "motor area" anteriorly. They stated at this time that the electrically excitable cortex extends in front of Campbell's precentral area (Brodmann's Area 4) and into his intermediate precentral area (Brodmann's Area 6). Four years after Campbell's publication, the studies of Holmes and Page May on "the exact origin of the pyramidal tract" appeared. These investigations found that in all types of mammals including man, hemisection of the spinal cord resulted in chromatolysis and further degenerative changes in the Betz cells; such changes were noticed in no other cortical cells. They therefore concluded that all pyramidal fibers arose from these giant cells. For the next 30 years this evidence became for most the indisputable proof of the origin of the pyramidal tract.

**Specificity of the Betz Cell.** Walshe<sup>54</sup> (1942) raises the question as to whether the Betz cell is truly a specific morphologic unit. He points out that different investigators have given widely different dimensions for these cells. If all of these dimensions were to be included, the cells would vary in size from 30  $\mu$  long and 12  $\mu$  broad to 120  $\mu$  long and 60  $\mu$  broad. Economo and Koskinas<sup>12</sup> have defined 5 different types of pyramidal cells in the cortex: (1) small pyramidal cells, varying in height (H) from 10 to 15  $\mu$  and in breadth at the base (B) from 7 to 10  $\mu$ ; (2) middle-size

pyramidal cells  $\frac{H}{B} = \frac{20 - 30}{10 - 20} \mu$ ; (3) large pyramidal cells  $\frac{H}{B} = \frac{30 - 50}{15 - 20} \mu$ ;  
 (4) giant pyramidal cells  $\frac{H}{B} = \frac{50 - 60}{25} \mu$ ; and (5) Betz giant pyramidal cells  
 $\frac{H}{B} = \frac{60 - 120}{40 - 60} \mu$ . According to Economo and Koskinas, many transitional

forms exist between these various types of pyramidal cells. Lassek<sup>32</sup> (1941) has made a careful study of the size of the large pyramidal cells in the fifth layer of Area 4, the cells being measured in square microns with a planimeter. As did Economo and Koskinas, Lassek concludes that there is great variability in the size of these cells. Of cells measuring between 900 and 4100 square microns, there is a gradual decrease in number from the smallest to the largest. The average size of the cell is largest in the upper third and smallest in the lower third. Walshe concludes, "Classification thus provides us with three categories of large pyramidal cell—Betz cell, simple giant cell and large pyramidal cell—but it seems clear that every possible transition form between the members of this conventional grouping is to be seen, not only in the adult cortex as reported by Economo and Koskinas, but also in the infant cortex as reported by Conel (1942). At one extreme we have the Betz cell with its numerous large Nissl granules, at the other the slenderer large pyramidal cell which only exceptionally contains distinct Nissl granules, but the series is continuous, and we can no longer accord the Betz cell the exclusive position we have hitherto given it as a specific entity with functions exclusive to itself. The Betz cell is no more than the largest and most massive member of the large group of pyramidal cells. . . . For purposes of description, classification is necessary, but having once made our groups, we are too ready to assume that we have discovered essential qualitative distinctions that may have no reality in nature."

Just as the size of the Betz cell is not clearly defined, neither is its area of distribution. Economo and Koskinas state that the posterior boundary of Area FA (Area gigantopyramidalis) is in the anterior wall of the fissure of Rolando, about 2 mm. from the floor of the fissure and the medial limits are in the paracentral lobule. The anterior limit and the lower limit near the fissure of Sylvius, however, are not readily demarcated. The largest Betz cells are found in the medial aspect of the area, *i. e.*, in the posterior portion of the paracentral lobule (leg area). Anteriorly and in the direction of the fissure of Sylvius, the size of the cells progressively diminishes. The cells, characteristically occurring in clusters, are not even distributed in Area 4. The simple giant cells and particularly the large pyramidal cells of Economo and Koskinas, however, extend well into Area FB (Area 6 of Brodmann). In the lowest portion of Leyton and Sherrington's electrically excitable cortex, no Betz cells which fit Economo and Koskinas' description are to be found. Betz cells are also described in the postcentral Areas PA, PB, and PC and PD of the parietal lobe.

Levin and Bradford,<sup>35</sup> repeating the retrograde cell degeneration studies of Holmes and Page May on monkeys, have attempted to solve the problem by enlarging the scope of the definition of the term Betz cell. After sectioning the pyramidal tract and studying the pyramidal cells of the cortex, the bulk of the retrograde degeneration is seen in Area 4 of Brodmann. Considerable degeneration, however, is also present in Areas 3, 1, 2 and 5 of the parietal lobes. Furthermore, it is not confined to the Betz giant cells, inasmuch as large and medium-sized pyramidal cells are also affected. They therefore suggest that the term "Betz cell" be modified to include cells of any size giving rise to corticospinal fibers.



**Relationship of Pyramidal Tract and Betz Cell.** As noted above, retrograde cell changes following pyramidal tract section are noted not only in Area 4 but also in Areas 3, 1, 2 and 5 of the parietal lobe. Levin and Bradford expressed the opinion that almost 20% of the pyramidal fibers (in *macaca radiata*) arise in the parietal lobe, the remainder arising in Area 4. Peele<sup>45a</sup> (1942) also states that the giant pyramidal cells of Areas 2 and 5b contribute to the corticospinal system. Marchi degeneration has been noted in the spinal cord following ablation of Area 6 (Kennard<sup>30a</sup>), evidence that this area also gives rise to corticospinal fibers. Levin<sup>34</sup> explains this degeneration on the basis of "heterotopic Betz cells" in Area 6. More recently (1944) Welch and Kennard<sup>65</sup> have pointed out that pyramidal tract degeneration differs markedly in animals in which the motor areas have been removed from those in which the hemisphere has been removed. "Thus, in the medullary pyramid there was complete degeneration of all fibers when one hemisphere had been removed, but following extirpation of Areas 4 and 6, the degeneration was only moderate. When the *postcentral gyrus* was added to the motor areas, the degree of degeneration lay between the two above extremes. In the dorsolateral tract of the cord removal of Areas 4 and 6 caused relatively slight loss of active fibers and even hemispherectomy did not produce complete degeneration. The existence within the 'pyramidal tract' of the cord of extrapyramidal fibers with cells of origin below the cortical level is thus indicated by the difference between total number of fibers showing degeneration in the tracts at medullary and spinal levels in the same animal."

The crowning blow to the work of Holmes and Page May has been dealt by Lassek<sup>32,33</sup> in a series of papers beginning in 1939, correlating counts of pyramidal tract fibers with counts of Betz cells. It was first shown that there are somewhat over 1,000,000 fibers in the human pyramidal tract, 61% of which are myelinated (Lassek and Rasmussen<sup>33</sup>). Most of the fibers are of small caliber, indicating that the bundle as a whole conducts slowly. In the past many of these fibers have been missed, largely because the main dependence has been on the Marchi stain which is ineffective in revealing small, unmyelinated fibers. Lassek has utilized the Davenport protargol method. Counts were then made of all of the large pyramidal cells in Area 4 from 900 to 4100 square microns in area. Approximately 34,000 cells were counted in the human. Thus it follows that the Betz cells can contribute but from 2 to 3% of the fibers in the pyramidal tract. Lassek expressed the belief that inasmuch as the large pyramidal cells of Area 4 are but a fraction of the total number of fibers of the pyramidal tract and the large caliber fibers in the pyramidal tract are also in the minority, these cells give rise to the rapid impulses carried by large caliber fibers. Approximately the same relationship exists between giant cell and pyramidal fibers in the rhesus monkey and in the spider monkey (*Atelus ater*). In the latter there appears to be no correlation between the number of these cells in various portions of the motor region and the ability to perform skilled movements. For, whereas it uses its thumbless hand poorly and has great dexterity with its tail, it has a higher percentage of giant cells in the lower third of Area 4 (arm area) than either the rhesus monkey or man.

Lassek has also described the changes in the histologic appearance of the pyramidal tract from infancy to old age. While apparently all of the axons are present during the first few months, they are small, delicate, uniform in caliber, crowded and possibly of a different chemical nature than when mature. At 8 months, about the time that myelinization

starts, a few axons accelerate in growth, while the remainder remain stationary. Presumably these are to become the large, myelinated axons of the adult. At 2 years, the pyramidal tract, while smaller, resembles that of an adult. In senility there is a decrease in the number and diameter of fibers. While myelinization has been stressed as the determining factor in the onset of function, Lassek expresses the belief that morphologic and chemical changes in the axons are also of importance.

The application of the method of retrograde degeneration has been brought to task by Lassek. He points out that not only do many pyramidal tract fibers remain intact above the site of the lesion but also that small nerve cells do not show chromatolysis. The large motor cells are probably the only ones in which changes may be noted following tract section. While Betz cells undergo shrinkage and loss of Nissl substance following pyramidal tract section, there is no retrograde degeneration of pyramidal neurones. This leads Lassek to the conclusion that the Nissl substance is not responsible for the nutrition and metabolism of the axon and shows that the retrograde method, employing the Nissl stain, does not prove that the giant cells give sole origin to pyramidal fibers.

**Termination.** It has long been taught that the pyramidal tract terminates directly upon the anterior horn cell (Flechsig,<sup>15</sup> 1876). A good deal of evidence had accumulated, even in the later part of the 19th century, that such was not the case. Both von Monakow<sup>44</sup> (1884) and Pick<sup>47</sup> (1898) had expressed the view that an intercalated neurone was present, its cell body lying in the dorsal portion of the spinal gray matter. Sharpey-Schafer, Lewandowsky and Rothman were all unable to detect pyramidal fibers ending around anterior horn cells. The differences in opinion may be attributed largely to the unsatisfactory staining methods that were available at the time.

Hoff<sup>27</sup> has employed the method of bouton degeneration in an effort to solve the enigma. It has long been known that synapses of axon terminals with cells in the spinal gray matter are characterized by the presence of Endfüsse or *bouton terminaux*, small looplike structures in close proximity to the cell body. Hoff has shown that these boutons undergo a characteristic degeneration following section of the axon to which they are endings. First, they swell and thicken, in the course of 3 days becoming enlarged granular masses. In from 4 to 6 days the boutons have completely disintegrated. Using this method, Hoff and Hoff<sup>28</sup> have studied the spinal gray matter following removal of the cortical motor areas. Following unilateral extirpation of Area 4, bouton degeneration for the most part (80 to 90%) occurs in the intermediate zone of the contralateral gray matter, while but a minority terminates in the ventral horn. They conclude that the pyramidal tract ends chiefly around internuncial cells in the intermediate region. They also note that following dorsal root section, the area of bouton degeneration overlaps that which is seen with cortical ablations. This confirms the statement of Ariens Kappers that corticospinal fibers terminate mainly on cells which are in direct contact with afferent, rather than efferent, fibers.

Using electrophysiologic methods, Lloyd<sup>38</sup> has arrived at somewhat the same conclusion as that of Hoff in regard to the termination of the pyramidal tract. The animals were first decerebrated at the collicular level. Stimulating electrodes were inserted into the pyramidal tract of decerebrate cats at the level of the trapezoid body. A lesion was made caudal to these electrodes, severing all descending and ascending pathways except the pyramidal tract. By means of micro-electrodes placed along

the pyramidal tract and in the gray substance of the spinal cord, it was possible to study the speed of impulses carried in the tract and to determine the number and location of synapses. The most rapid conducting fibers of the pyramidal tract had a velocity between 60 and 65 meters per second. Many slower conducting axons were also present; dispersion of a volley, synchronous at the medullary level, continued to produce a discharge of pyramidal impulses lasting many milliseconds. This closely parallels Lassek's description of the variation in size of pyramidal tract fibers—the larger, fast-conducting fibers being outnumbered by the smaller, slower conducting ones. Small nuclear elements, in close proximity with the pyramidal tract (external basilar region), appeared to constitute the initial internuncial relays. A second internuncial relay appeared to exist in the intermediate gray region (intermediate gray nucleus of Cajal) which synapses with the motoneurone (anterior horn cell). It also appeared likely that pyramidal fibers have synapses with the solitary large cells of the dorsal horn, sensory in character. All the effects of stimulation were of an excitatory nature. No evidence was found that the pyramidal tract is of any importance in producing inhibition.

It can therefore be concluded that the pyramidal tract is in a position not only to influence the motor neuron but also the sensory impulses entering the cord over the dorsal roots.

**Consideration of Pyramidal Tract Function From Lesions at Decussation and in Spinal Cord.** The assumption that spastic paralysis, hyperreflexia and pathologic reflexes follow lesions of the pyramidal tract has been so deeply installed in neurologic thinking that these findings are often referred to as "pyramidal tract signs." These suppositions are based largely on clinical material, in which lesions rarely, if ever, are confined purely to the pyramidal or corticospinal system. By definition the pyramidal tract contains those fibers that pass through the medullary pyramids. It is only in this location that the fibers exist as a segregated unit. The pyramidal tracts may be approached surgically through an incision in the anterior midline of the neck after removing a portion of the basiocciput. Recently such experiments have been reported by Marshall<sup>39</sup> and by Tower<sup>51a</sup> in the cat, and by Tower<sup>51b</sup> in the monkey.

Marshall stated that most of his cats had little difficulty in walking following pyramid section, even on the second postoperative day. The animals, in general, suffered less impairment than those in which the motor areas have been removed. Marshall described an "initial symptomatology," which includes (1) diminished or absent contact placing reactions, (2) reduced visual placing reaction, (3) difficulties in walking a ladder or narrow tract, (4) delayed hopping reactions, (5) increased resistance to passive flexion, with the animal suspended in a sling, (6) diminished resistance to passive extension, (7) spontaneous postural abnormalities, (8) non-correction of abnormal postures imposed on the feet, (9) occasional transient staggering, (10) a certain stiffness in gait, (11) a heavy and awkward landing after jumping down from a height and (12) reduced activity and slowness in motion. A degree of recovery took place from all of the symptoms; sometimes it was complete. "*There was no constant set of symptoms remaining over at the end of the period of observation of 2 to 3 weeks.*"

Tower was unable to discover any spasticity in cats in which the pyramids had been sectioned. In her study of pyramidal lesions in the monkey, she described the presence of a contralateral "hypotonic paresis" (quantitatively less than a "flaccid paralysis"). This paresis affected all so-

matic function, though not equally, and some visceral function. Its outstanding features were diminished muscle tone; diminished cutaneous reflexes; slow, full tendon reflexes restricted to the muscles stimulated; lowered skin temperature; defective initiation and execution of all performance by skeletal musculature with elimination of non-stereotyped components, and elimination of all discrete usage of the digits. In general, the threshold of reflexes was raised and they were weak and sluggish. The hypotonia was most noticeable in the hip and shoulder musculature. Following bilateral section, the hypotonia was also marked in the musculature of the neck, back and thorax—"axial hypotonia." The animal with bilateral pyramidal section, unable to compensate with a healthy side as the animal with unilateral section, developed a greater range of movement than was seen in the paretic extremity of the latter. This movement was highly volitional and purposive. It was carried out slowly and laboriously; ready fatigability was present.

Tower draws the following conclusions regarding the function of the pyramidal tract: "It is organized in complexity to match virtually the full range of activity, from simple tonic functions wherein it merely assists, to complicated performances which are primarily its responsibility. Although traditionally, the pyramidal system has been considered 'the voluntary motor pathway,' this is too sweeping. An impressive capacity for voluntary movement survives pyramid section, especially if the lesion be bilateral, forcing the issue. Conversely, some activities eliminated by pyramidal lesion, for example the contact placing reactions, must be considered, if not involuntary, at least highly automatic. By virtue of its tonic action on the spinal cord, pyramidal function must assist all somatic motor activity, if not, indeed, all motor activity of the waking animal, at whatever level initiated, even the spinal reflex level, without regard for the voluntary or automatic quality of particular acts. As the agent of lability, however, the pyramidal tract makes a unique contribution to total performance. Together, the all-pervading, and the discriminating qualities of corticospinal action afford the cerebral cortex that influence in virtually all realms of final motor action, and that minuteness of control which determine its effectiveness as an agent of choice. In this service of choice the pyramidal tract is unquestionably the outstanding, though not the exclusive, voluntary motor pathway."

Cannon, Beaton and Ranson<sup>7</sup> have recently reported their results on the interruption of the lateral corticospinal tract in the monkey. Additional descending fibers than those of the pyramidal tract, however, were interrupted. In spite of this, the paresis was characterized by hypotonicity, hypoactive reflexes and the absence of clonus—much the same findings as in Tower's monkeys. The paresis was more prominent in the upper than the lower extremity and more extreme in the distal rather than the proximal musculature.

Putnam's<sup>48</sup> treatment for paralysis agitans by section of the lateral pyramidal tract in the cord has given information regarding the lesion in the human. While the results are confused by the presence of additional neurologic deficit and the probable involvement of other descending pathways, the patients appear to suffer less disability than Tower's monkeys and retain discrete digital movement. This may be due to lack of involvement of all pyramidal fibers in the cord section. In contrast, to Tower's monkeys, some of the patients have exhibited slight spasticity and hyperreflexia.

All of these investigators agree that pyramidal section does not result

in a lasting spastic paralysis. It follows, then, that the enduring spasticity and paralysis so frequently observed in the human following a capsular thrombosis, for instance, is not due solely to interruption of corticospinal fibers as has been commonly attributed.

**Pyramidal Tract and Cortex:** "Motor Area," "Premotor Area," "Suppressor Areas, Parietal Lobe; Relationship of Basal Ganglia. "Motor area," "Area 4 of Brodmann," and "area pyramidalis" have been used as synonymous designations. From the early cytoarchitectonics of Campbell, attempts have been made to define motor cortex histologically rather than physiologically. Obviously the terms "motor area" or "motor cortex" only have meaning in terms of motor function. The attempt to force them into a histologically more or less well-defined area, plus the previously mentioned attempt to restrict the origin of the pyramidal tract to a specific type of cell in the fifth layer of this area has resulted in an overly simplified picture of motor function.

The physiologic methods at our disposal for the study of cortical motor function include (a) stimulation experiments, either mechanical, chemical or electrical, the latter being preferred, and (b) ablation experiments.

*Cortical Electrical Stimulation.* The early stimulation experiments of Fritsch and Hitzig<sup>19</sup> (1870), Ferrier<sup>14</sup> (1873), and Beever and Horsley<sup>2</sup> established the existence of a motor area in a variety of mammalian cortices. The later, more refined studies of Leyton and Sherrington<sup>36</sup> (1917) on the cortex of chimpanzee, orang and gorilla further elaborated the various components of the cortical motor area. As was noted previously, in their earlier publication (1903), the electrically excitable cortex was limited to Area 4, or Campbell's precentral area. In the 1917 publication, however, "The motor field's boundary seems to lie, especially in its lower two-thirds, farther forward than does Campbell's precentral area. The anterior border, as determined by faradization is, however, not a sharp one, and its situation seems to vary somewhat from specimen to specimen. As placed by us, it certainly appears to lie for the most part in the intermediate precentral area of Campbell. Opposite the 'arm area' it lies not far behind the anterior border of the intermediate precentral area, but opposite the 'leg area' it lies very much further behind the anterior limit of the intermediate precentral area, although in front of the anterior limit of the pure precentral area of Campbell." Thus Leyton and Sherrington include a portion of Area 6 in their "motor area."

Modern studies of the electrically excitable cortex of the human include those of Foerster<sup>16</sup> (1936), Penfield and Boldrey<sup>46</sup> (1937) and Scarff<sup>49</sup> (1940).

Foerster, in plotting the motor points of the cortex, found that both Area 4 and Area 6 $\alpha$  (using the Vogts' terminology) respond to electrical stimulation by the isolated movements of a part of the body or of a single segment of the extremities. But to obtain these effects from Area 6 $\alpha$  a considerably stronger stimulus is needed than in Area 4. Following undercutting the cortex between this area and Area 4 the isolated movements are abolished. Strong faradic stimulation of Area 6 $\beta$  (the rostral portion of Area 6) produced complex mass movements on the contralateral half of the body. Foerster has called this area (6 $\beta$ ) the "frontal adverse field," because of the production of adverse movements, that is turning of the head, eyes, and trunk in the opposite direction. When Area 6 $\alpha$  was rendered impotent in the production of isolated movements by undercutting between it and Area 4, it responded with the same type of mass movement as did Area 6 $\beta$ . Stimulation of Area 6 $\alpha$  of the Vogts, lying rostral to the "face area" of Area 4, resulted in sustained,

rhythmic and coördinated movements of lips, tongue, mandible, pharynx and larynx. Isolated movements were also produced by stimulation of the postcentral gyrus (Areas 3-1-2 of the parietal lobe). As in the case of Area 6a $\alpha$ , these movements were produced at a higher threshold than those from Area 4 and were abolished by undercutting them between them and Area 4. Stimulation of Area 5, the superior parietal lobe, and of Area 22 in the temporal lobe gave rise to the same mass movements as noted following stimulation of Area 6a $\beta$ . Foerster concluded that isolated movement from Area 6a $\alpha$  and Areas 3-1-2 "depend upon the integrity of Area 4 and its motor pathway, the pyramidal tract. So we can say that the Area 4, the *area pyramidalis*, is the specific area for isolated innervations." The more complex movements arising from Areas 6a $\beta$ , 5 and 22, "extrapyramidal cortical areas," descend along other, extrapyramidal, pathways.

Penfield and Boldrey (1937) have made some modifications in the cortical motor points of Foerster. "It is seen that toes begin at the top [of the fissure of Rolando] and the members follow in order as though representing a man hung upside down, but that thumb is followed by the head as though the head and neck were erect and not inverted." The areas for the thumb and lips was "very large," for the trunk "quite small," and for the legs and head "very small." Discrete responses were obtained from the postcentral gyrus, though less frequently than from the precentral gyrus (Area 4). They failed to verify the presence of motor responses described by Foerster in Areas 6a $\beta$ , 5 and 22 and feel that these may have been epileptiform discharges. "Thus our results from stimulation resemble those of Grünbaum and Sherrington in the chimpanzee except that they got no responses from the postcentral gyrus." Recently (1940), it should be added, Hines<sup>26b</sup> reports a number of motor points in the postcentral gyrus of the chimpanzee. Furthermore, Peele<sup>45b</sup> (1944) states that it is possible in the monkey to delimit Areas 5 and 7 in the posterior portion of the parietal lobe from Areas 3, 1 and 2 in the anterior portion or postcentral gyrus, according to the type of movement elicited and the threshold. Stimulation of Areas 3-1-2 resulted in flexion movements while stimulation of Areas 5 and 7 resulted in elevation of the contralateral shoulder and protraction of the entire upper limb.

Scarff<sup>49</sup> (1940) has criticized the view that the human motor area is similar to that of the chimpanzee. He has expressed the belief, on the basis of electrical stimulation, that the motor strip in man has migrated upwards. "The primary motor area for the upper extremity commonly extends upward on the lateral surface of the cerebral hemisphere as far as its superior mesial border, while the leg, as a rule, is represented only on the mesial surface of the cerebrum." This may explain the infrequency of movements in the lower extremities and the small area allotted to the leg area by Penfield and Boldrey.<sup>46</sup> These investigators did not stimulate the mesial surface of the hemisphere. This upward "migration" of the motor strip in man is possibly influenced, Scarff states, by the elaboration of complex functions of the upper extremities and the acquisition of speech.

"Premotor Area" versus "Motor Area." Removal of Area 4 of the chimpanzee according to Fulton<sup>20</sup> results in immediate flaccid paralysis of all movements of the contralateral arm, the distal musculature being affected more than the proximal. While considerable improvement in function is noted following the operation, precise digital movements do not return. Although the paralysis is essentially flaccid in character, a

phase of digital spasticity has been noted between the 3rd and 5th post-operative week (Denny-Brown and Botterell<sup>8</sup>). The tendon reflexes disappear initially but soon return, and usually become somewhat hyperactive. Dorsiflexion of the great toe appears: eventually there is marked atrophy of the contralateral musculature, especially proximally.

When Area 6 is removed, the neurologic deficit presents a picture that is significantly different. This consists of transient contralateral paresis, permanent awkwardness with skilled movements, forced grasping, spasticity, and reflex changes. The paresis is slight and is present but for a few days following the ablation. The permanent defect with skilled movements is manifest in such actions as approximating the thumb and index fingernail or picking up a hair. Forced grasping is said to be due to withdrawal of extrapyramidal inhibitory impulses from this area which releases subcortical centers. It consists of the slow flexion of the digits in response to gentle contact with the palmar or plantar skin and is present in both primates and man following lesions of Area 6. It disappears in the course of a week in the monkey and in 2 weeks in the chimpanzee. Similarly, the spasticity and the moderate increase in tendon reflexes are transient events with ablations limited to this area, as are the presence of the Rossolimo toe reflex and the Hoffmann finger reflex. In spite of the fact that lesions of Area 4 result in an essentially flaccid type of palsy, it is only when removal of this area is added to that of Area 6 that all of the deficits described above become permanent and marked. The reflex changes are conspicuous and enduring and are essentially those which accompany the spastic state in man. The tendon reflexes are markedly increased, and pathologic reflexes (Babinski, Chaddock, Rossolimo, Hoffmann, Mendel-Bechterew, Gonda) are present. Forced grasping also becomes permanent and predictable.

Fulton chooses to call Area 6 the "premotor area" in contrast to Area 4, the "motor area." The justification for the use of this term is based on the different findings following ablation of each of the areas, the absence of Betz cells in Area 6, the decreased excitability to electrical stimulation of Area 6, and the loss of isolated motor responses from Area 6 after an incision is made between the two areas. It is assumed that isolated volitional movements depend upon Area 4 and its projection, the pyramidal tract. Gross movements, however, may originate from the premotor area and be transmitted over extrapyramidal pathways.

Walshe<sup>54</sup> has raised a number of objections not only to the term "premotor area" but to Fulton's concept of a dual motor mechanism as outlined above. These objections are summarized: (1) There is no sharp anatomic division between the two zones. As shown by Economo and Koskinas, the "hairline divisions" between Areas 4 and 6 do not rest on any certain anatomic foundation. (2) Stimulation experiments in both anthropoids and man (Leyton and Sherrington,<sup>36</sup> Foerster,<sup>16</sup> Penfield and Boldrey<sup>46</sup>) have given no indication of a difference in function between the two areas. "As the stimulating electrode passes anteriorly across the cortex of Area 4 (FA) on to that of Area 6 (FB), the character of the motor responses and the strength of stimulus necessary to evoke them show no change whatever except at the anterior fringe." The concept of discrete movements being dependent on Area 4 and of widespread movements on extrapyramidal projections from Area 6 is also attacked. Widespread movements obtainable from Area 6 may be the result of the increased strength of stimulus rather than any physiologic difference inherent in the two areas. As Foerster<sup>16</sup> has shown, wide regions of the cortex

can be made to yield movements on maximal stimulation. This does not prove that these areas normally give rise to such movement. "All that can be elicited from this supposed premotor cortex can also be elicited from the rest of the motor cortex if this be sufficiently strongly stimulated." (3) The evidence from ablations of Areas 4 and 6 is in such conflict that no conclusions may be drawn. He cites the occasional increase in reflexes and hypertonus in some of Fulton's animals in which Area 4 was removed and the lack of hypertonia in others in which Area 6 was removed. Denny-Brown and Botterell<sup>8</sup> have described an initial flaccidity and the subsequent development of spasticity and hyperreflexia in monkeys with only Area 4 removed. Foerster<sup>16a</sup> has said: "So far as conclusions can be drawn from these observations, they seem to demonstrate that the motor disturbance resulting from isolated destruction of Area 4 in man does not differ to a detectable degree from that due to destruction of both Areas 4 and 6aa." (4) Walshe argues that section of the pyramid in the medulla must interrupt both pyramidal and extrapyramidal fibers and therefore, if Fulton's hypothesis is correct, should lead to spasticity. The pyramidal tract lesions of Tower,<sup>51</sup> however, have resulted in a flaccid paralysis. This, according to Walshe, proves the incorrectness of the dual motor mechanism hypothesis. He fails to consider that the extrapyramidal tracts, which Fulton *et al.* believe to be responsible for spasticity, may course outside of the medullary pyramid. The postulation is made that interference with short projection tracts arising in Areas 4 and 6 (*i. e.*, the precentro-pontine tract, cortico-rubral and cortico-nigral tracts) are the responsible agents. "The extension of this field of cells well into Area FB (Area 6) in which its focus may well lie, may account for the marked hypertonus that ensues when ablations encroach upon the region immediately anterior to the motor cortex." As far as can be made out, the work of Fulton and his colleagues (see Kennard,<sup>30b</sup> 1944) does not contradict this point of view. It may well be that Walshe and they are actually not far apart in their views but that the difference is mainly one of terminology.

*Suppressor ("Strip") Areas.* Revision of the conclusions of Fulton and his collaborators have been necessitated by the work of Marion Hines<sup>26a</sup> (1937). She has shown that ablation of a slender strip of cortex in the anterior portion of Area 4 gives rise to all of the phenomena described by Fulton in his "premotor area syndrome" except that of forced grasping. In the rhesus monkey both release phenomena and paralysis appear in the extremity opposite the side of the lesion. The paralysis disappears, for the most part, within 2 weeks. Muscular hypertonus, clonus and hyperactive reflexes remain. As in the human with spastic hemiplegia, the maximal hypertonus is in the flexors of the elbow, the extensors of the knee and the adductors of the thigh. This "strip area" of Hines is about 3 mm. in width. "It passes through the superior precentral fissure. It extends from the superior precentral fissure to the fissura calloso-marginalis on the medial surface, following throughout at equidistance the curve of the central fissure." Isolated ablation of Area 6 by Hines leads to none of the findings described by Fulton for his "premotor syndrome" except the presence of the grasp reflex.

When both the "strip" area (4s) and Area 6 are removed, the distribution of muscular hypertonus changes and the "clasp knife" type of resistance seen with Area 4s lesions disappears. The hypertonus is present and similar in both protagonists and antagonists (flexors and



extensors) in the proximal joints of all four extremities. Brisk reflexes are present initially but gradually subside.

When the posterior portion of Area 4 is removed, a picture similar to that described by Fulton for removal of Area 4 appears. No spasticity or hyperreflexia is present. Paralysis is about complete for 2 days, then gradually disappears in 2 months. After total removal of Area 4 (including 4s), the contralateral limbs are not used to initiate voluntary movement but merely aid or follow those of the other extremities. Hyperreflexia, clonus and hypertonus are present, but the latter is not as marked as when the lesion is restricted to the strip area.

From this work and from stimulation experiments upon animals in which the medullary pyramids have been sectioned (Tower and Hines,<sup>52</sup> Tower<sup>51</sup>), Hines concludes that Area 6 is responsible for inhibition of flexor patterns (grasp reflex) and that the strip area (4s) is responsible for inhibition of extensor patterns. "The removal of the anterior division of Area 4 (the "strip" area) gave a maximum loss of inhibition of extension; its stimulation, relaxation of tonic extension. The removal of Area 6 gave the grasp reflex; its stimulation relaxation of tonic flexion including the grasp. The removal of both of these areas results in the release of two opposing inhibitions which tend to neutralize each other, such that differential resistance to passive movement is lost; and resistance becomes distributed equally between protagonists and antagonists."

As demonstrated by these experiments and those following section of the medullary pyramids by Hine's co-worker, Tower,<sup>51</sup> spasticity and paralysis are distinct entities, the former being transmitted over extrapyramidal pathways, the latter—at least in part—over pyramidal pathways.

In a series of important experiments, Dusser de Barenne and McCulloch, later with Garol and Bailey,<sup>1,9,10,23,24,40</sup> have produced evidence that parallels that of Hines in regard to the function and connections of the strip area (4s). They have also shown that other "strip areas" with similar functions are present in the cortex of the macaque and the chimpanzee and have succeeded in tracing the pathways from these areas into the basal ganglia. Dusser de Barenne long ago demonstrated that when strychnine is applied locally to the central nervous system, disturbances are set up which travel along axons in the direction of normal conduction, not antidromically. These disturbances are diminished, dispersed and delayed when they pass through synapses. They may be recorded by means of electroencephalographic apparatus. It is therefore possible to delimit the axonal distribution of nerve cells in any gray mass of the central nervous system. This method has been termed "physiological neuronography."

Dusser de Barenne *et al.* have shown that stimulation of the anterior portion of Area 4 (4s) results in the diminution not only of the spontaneous electrical activity of Area 4 but also of peripheral motor responses. This "suppression" has a latent period of about 4 minutes. It has been shown using the strychnine method that suppression of electrical activity is not due to direct connections between Area 4s and Area 4, but rather to impulses which travel down to the caudate nucleus. From the caudate nucleus, the impulses are carried back to the cortex by means of an indirect pathway involving thalamo-cortical projections. Four other "suppressor areas" have also been described, 8s, 2s, 19s, and 24s. "The characteristic responses obtained from electrical stimulation of such suppressor areas, varying somewhat with the duration and intensity of stimulation, are as follows: (1) a lessening of existing muscular tension throughout the

body, particularly on the contralateral side; (2) a pronounced rise in threshold to electrical stimulation of Area 4; (3) a holding in abeyance of a motor after-discharge induced by stimulation of Area 4; (4) a failure to produce, in the absence of summation or recruitment, a peripheral motor response; and (5) a return of normal electrical excitability following suppression. These phenomena are abolished by undercutting of the area, e. g., Area 4s." Suppression of motor response in man from stimulation of a circumscribed area of cortex has just been reported by Garol and Bucy.<sup>23</sup>

*Parietal Lobe and Motor Function.* The histologic evidence of giant pyramidal cells in the postcentral area, the work of Levin and Bradford<sup>35</sup> showing that about 20% of pyramidal fibers originate in Areas 3, 1, 2 and 5, and the descriptions of motor responses to electrical stimulation of the parietal lobe have been cited. No true paralysis has been reported with lesions confined to this lobe. Brodmann<sup>4</sup> and Ferraro and Barrera<sup>13</sup> have noted hypotonia following removal of the postcentral gyrus. Kennard and Kessler,<sup>31</sup> in a study of motor performance following parietal lobe ablations, have described a motor deficit characterized by disuse, diminished resistance to passive movement, non-persistent hyporeflexia and awkwardness of movement, the latter apparently being the result of losses in the sensory sphere. More recently Peele<sup>45b</sup> has described a "loathness of movement" in the macaque. Removal of Areas 3-1-2 affected the contralateral leg and arm equally. Removal of Area 5 affected the leg in particular, and removal of Area 7 the arm. Hypotonia was consistently present for as long as a year, especially involving the proximal muscles of both arm and leg. Tendon reflexes were more difficult to elicit, were slower and had an increased excursion.

In spite of the evidence that removal of either Area 4 or the postcentral gyrus (Areas 3-1-2) independently result in hypotonia or flaccidity, both Walker (cited by Fulton<sup>20</sup>) and Welch and Kennard<sup>55</sup> assert that combined lesions lead to spasticity. Welch and Kennard apparently attribute this curious phenomenon to the severance of additional extrapyramidal pathways, although they state that only relatively small extrapyramidal contingents arise from these areas. "All evidence presented is thus in harmony with the statement of Fulton who writes '... the intensity and duration of spastic resistance are functions, not of any area, but of the extent of interruption of extrapyramidal cortical projections.'" Certainly the determination of the presence of flaccidity and spasticity is no simple arithmetical function. The flaccidity of the pyramidal lesion is not a nullifying influence upon the spasticity of the extrapyramidal lesion. To further complicate matters, Browder<sup>5</sup> reports that ablation of the human postcentral region reduces rather than enhances preëxisting spasticity.

*Basal Ganglia and Motor Function.* As might have been predicted from Hines' demonstration of a cortical inhibitory area (4s) and the subsequent demonstration by "physiologic neuronography" of connections between it and the caudate nucleus, recent evidence shows that one of the main functions of the basal ganglia is inhibition of cortically induced movements. Stimulation experiments upon basal ganglia structures have failed to give definite results. Mettler,<sup>41a,42</sup> as others before him, failed to produce any responses upon simple stimulation of either caudate, putamen or claustrum in the cat. When, however, phasic (repetitive) movements were produced by cortical stimulation, subsequent stimulation of these structures produced definite effects. Stimulation of the

caudate nucleus led to inhibition of these movements. Similar, though milder, results were obtained by stimulation of the putamen and claustrum. Freeman and Krasno<sup>18</sup> later showed that spontaneous activity was inhibited by striatal stimulation. While this inhibitory function appears to act bilaterally, there has not been general agreement as to the predominant side which is influenced. Mettler believed that the contralateral side is especially involved, while Freeman and Krasno believed homolateral inhibition is the more marked. Simple stimulation of the globus pallidum by Mettler resulted in tonic, postural contractures on the ipsilateral side, even when the cortex was removed or the pyramids cut. Following the production of cortically induced movement, stimulation of the globus pallidum converted this movement into a state of plastic tonus. Portions of the limb could be placed in any position and would remain fixed during the period of stimulation. In addition, relaxation time was greatly prolonged. Mettler therefore concludes, "The pyramidal and extrapyramidal systems constitute a closely organized and interrelated functional unit. Not only the final motorneuron but also the cortex forms ground common to these two so-called 'systems.' In this arrangement the striatum (caudate and putamen) occupies the position of an inhibitory mechanism. Stimulation of it produces inhibition and removal of it engenders evidences of motor release. It stands on the one hand between the cortex and the final common path as part of the route through which the cortex may exert an inhibitory function and, on the other hand, it operates between the thalamus and lower motor mechanisms in the automatic inhibition incident to 'unconscious' activity. The pallidum, as contrasted with the striatum, is a positive motor mechanism through which associated movement patterns involving the larger muscle masses . . . are involved in tonic discharge."

*Combined Lesions of "Motor" Area and Basal Ganglia.* Lesions confined to basal ganglia have given equivocal results, as far as resistance to passive movement and reflex changes are concerned. (Discussion of the abnormal movements such as tremor and chorea from these lesions is omitted here.) Liddell and Phillips<sup>37</sup> have reported a slight but persistent hypertonia of the extensor muscles in the contralateral limbs. This has not been seen by Mettler<sup>41a</sup> or Kennard.<sup>30b</sup> Kennard and Mettler agree, however, in spite of the absence of spasticity with lesions restricted to basal ganglia, when such lesions are added to cortical ablations, there is a substantial increase in the spasticity. In a recent paper (1943) Mettler<sup>41b</sup> discusses in detail the results of such lesions in primates. With unilateral frontal decortication, paresis and spasticity are so mild "that they may be imperceptible to the inexperienced observer." With complete unilateral decortication there is no specific additional paralysis. When the striatum (caudate and putamen) is added to the decortication, there is little further loss of motor capacity except for loss of monomanual feeding with the involved hand. There is much less spasticity after hemidecortication alone than after removal of both cortex and striatum. In addition there is a reduction of the threshold and an increase in amplitude of the patellar reflex with combined removals. Only when the defect in the basal ganglia is extremely large, reaching the level of the posterior commissure, does paralysis become almost complete, and spasticity is of such a degree as to give rise to fibrous contractures.

*The Plantar Reflex (Babinski Sign).* Until recently there has been general agreement that the Babinski sign, dorsiflexion of the great toe following plantar stimulation, occurs only as a result of pyramidal tract

interruption. Fulton<sup>20b</sup> states that it is part of a generalized flexor reflex such as is seen in its full form in spinal animals. The typical response may be seen in the chimpanzee after removal of the foot area, according to Fulton and Keller.<sup>21</sup> The same observers stated that the typical Babinski sign does not occur in lower forms, such as the monkey. The absence of the response in Tower's monkeys in which the medullary pyramids were cut was explained on this basis. In 1942 Forster and Campbell<sup>17</sup> succeeded in producing the Babinski sign in a number of rhesus monkeys in which extensive cerebral damage had been produced. They concluded that extensive, bilateral cortical lesions may give rise to the phenomenon in the monkey and that the projection fibers may travel down the ventral columns of the spinal cord. In an extensive study of lesions of the brain stem in primates, Mettler<sup>41c</sup> (1944) has noted the pathologic toe response in animals without pyramidal tract involvement. Destruction of the rubro-spinal system was found to be most consistently associated with the Babinski response, even in the absence of paralysis. Mettler therefore suggests that this sign indicates extrapyramidal rather than pyramidal damage.

Additional evidence that the sign of Babinski and other so-called "pyramidal signs" may be the result of lesions outside the pyramidal tract has been presented by Lassek<sup>32h</sup> (1944). He studied the pyramidal tract in 119 clinical cases with "pyramidal signs," 100 of these having a Babinski response. In only 14% was there any observable evidence of destruction to this tract, and in only 6.7% was it complete. The Babinski sign was present in 88 of 102 cases in which the pyramidal tract was observed to be normal. A tumor mass in apparently any part of the cerebrum produced motor loss with either a transient or permanent Babinski sign. Lassek, therefore, could find no correlation between the Babinski sign and pyramidal tract damage.

**Conclusions.** Researches during the past decade have contributed a vast amount of information regarding the pyramidal tract, its relationship and its function. Much of this information is inconclusive and contradictory. Some of it has necessarily been destructive in the sense that it was mainly directed at disproving ancient dogma concerning the pyramidal tract, handed down through a number of medical generations.

The neurologist is placed in the unenviable position of being less sure about his knowledge of the motor system and less sure of his interpretation of motor deficits than he formerly was. It is no longer possible for him to state with any degree of assurance that spasticity, hyperreflexia and pathologic reflexes are certain evidences of pyramidal tract disease.

In spite of the almost inevitable confusion surrounding an adolescent field of investigation, certain conclusions may be drawn.

1. The pyramidal tract does not arise solely from the Betz cells of Area 4. These cells, not well-defined units in themselves, are far outnumbered by pyramidal axons. It seems most likely, though not definitely proven, that not only do Area 6 and the areas of the postcentral gyrus give rise to these fibers, but that they come from widespread cortical areas. It also seems likely that the pyramidal tract in the spinal cord (lateral corticospinal tract) is mixed with fibers originating in subcortical nuclei.

2. The pyramidal tract terminates for the most part, not upon the anterior horn cell (motoneuron) of the spinal cord, but upon internuncial neurons in the central gray matter. Here they are in a position to influence not only the lower motor neuron but also all sensory impulses entering

the cord over the dorsal roots. The physiologic implications of this are yet to be adequately analyzed.

3. Neither partial or total section of the pyramidal tract gives rise to spastic paralysis. Decreased resistance to passive movement without hyperreflexia appears to result.

4. The pyramidal tract is not the sole voluntary motor pathway. It is, however, apparently essential for the complete preservation of isolated, intricate and skilled movements.

5. The pyramidal tract is not an inhibitory pathway, as was propounded by Charcot. Inhibition, rather, is the function of extrapyramidal pathways originating in certain areas of the cortex, the caudate nucleus and probably elsewhere. Stimulation of these areas results in the inhibition of voluntary activity.

6. From the evidence available at present, it seems likely that hyperreflexia and spasticity are release phenomena from lesions of extrapyramidal pathways. This evidence is not completely convincing. Enduring hyperreflexia and spasticity are only seen with combined pyramidal-extrapyramidal lesions. The absence of hyperreflexia in basal ganglion syndromes such as paralysis agitans has not been elucidated.

7. The cerebral cortex is not divided into purely pyramidal and purely extrapyramidal areas just as it is not divided into purely motor and purely sensory areas. This complicated, overlapping functioning has not made analysis of the "motor cortex" easy. While Area 4 is undoubtedly the most significant in the production of movement, Area 6 and portions of the parietal lobe also play a rôle. The type of neurologic deficit which follows any cortical lesion appears to depend upon the relative impairment of pyramidal and extrapyramidal projections. Lesions of the posterior portion of Area 4 apparently lead to defects in isolated, precise movements, without spasticity or markedly increased reflexes. Lesions rostral to the posterior portion of Area 4 give rise to the release phenomena of spasticity and hyperreflexia. Combined lesions of Area 4 and the post-central gyrus lead to similar findings. There is some evidence that Area 4s is responsible for inhibition of extension patterns and Area 6 for inhibition of flexor patterns.

8. The most marked and enduring spastic paralyses are seen when not only cortical motor projections are abolished but also large portions of the basal ganglia.

9. While a good deal of evidence still favors the concept that the Babinski response is due to a lesion of the pyramidal tract, this remains a moot question.

10. The suggestion is made that when one is confronted with the findings of hyperreflexia, clonus, spasticity and pathologic reflexes, that the term "pyramidal tract signs" be abandoned. As a substitute, the less specific "upper motor neuron signs" may be used, if this is meant to include both pyramidal and extrapyramidal pathways.

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## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 21, 1944

**Repair Following Tucking Operations on the Extra-ocular Muscles.\***  
**K. S. CHOUKE** (Department of Anatomy, Graduate School of Medicine, University of Pennsylvania). Thirty-eight tucking operations were performed on either the superior rectus or the lateral rectus muscle of 20 adult dogs. Dogs varied in weight from 7 to 19 kg. The animals were sacri-

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ficed from 1 to 155 days after the operation. For anesthesia, sodium amytal was used intraperitoneally or intravenously.

The muscle union was accomplished by organization of fibrin and by granulation tissue. This observation confirms the findings of Carroll and Blake, and of Gifford.

After a tucking operation the 2 adjacent sides of the loop of muscle join together by means of fibrous connective tissue. The side of the muscle nearest the eyeball quite often, but not always, becomes attached to the sclera by fibrous connective tissue. The process of repair of extra-ocular muscles in the dog is essentially similar to that of the skeletal muscles elsewhere in the body. The time required for the completion of repair of extra-ocular muscles is slightly longer than that for general skeletal muscles of the same animal. The continuity of the muscle is preserved after the tucking operation, as evidenced by response to electrical stimulation.

The author gratefully acknowledges the preparation of the microscopic sections and the facilities for operation provided by the Harrison Department of Research Surgery, University of Pennsylvania, under the direction of Dr. I. S. Ravdin.

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**Chemotherapeutic Properties of Streptomycin.** HARRY J. ROBINSON, OTTO E. GRAESSLE and DOROTHY G. SMITH (Merck Institute for Therapeutic Research, Rahway, N. J.). Recently we described the chemotherapeutic properties of streptothricin, an antibiotic agent isolated from a soil actinomycetes by Waksman and Woodruff. This agent proved to be highly active against gram-negative bacteria and pathogenic fungi (H. J. Robinson, O. E. Graessle, and D. G. Smith) but, unlike penicillin, streptothricin produced certain toxic effects in a variety of animal species. During the course of the study with streptothricin, a second agent was isolated by Schatz, Bugie and Waksman from *A. griseus* and was named streptomycin. We have studied *in vitro* and *in vivo* the pharmacologic, toxicologic, and chemotherapeutic properties of streptomycin, and the results of this investigation are presented in the following:

Streptomycin is well tolerated by mice and rats when given parenterally in doses of 50,000 units per kg. daily over a period of 1 month. Likewise, monkeys also tolerate large doses of the drug without showing any untoward reactions.

Streptomycin, *in vitro*, is active against a variety of gram-negative and gram-positive bacteria, but not against fungi. Members of the gram-negative enteric group of microorganisms and related genera, including Eberthella, Salmonella, Escherichia, Shigella, Klebsiella, Brucella, Pasteurella, and Proteus, are particularly sensitive to streptomycin, while certain strains of *Pseudomonas aeruginosa* show considerable resistance. Of the gram-positive organisms, strains of *Strep. hemolyticus*, *Staph. aureus* and *D. pneumoniae* are sensitive to streptomycin, whereas all members of the spore-bearing anaerobic group are highly resistant. Experiments in mice gave essentially the same results, subcutaneous doses of 100 units per mouse protecting against 10,000 lethal doses of most of the foregoing bacteria.

Streptomycin is most effective when given parenterally, although it also protects mice infected by intraperitoneal injection when administered by mouth. Examination of the feces of mice fed streptomycin shows that adequate doses sterilize the gastro-intestinal tract insofar as lactose-fermenting organisms are concerned. The total microbial population of the feces is also reduced considerably.

Following parenteral administration approximately 70% of the drug appear in the urine within 5 to 6 hours after the injection. In order to maintain blood concentrations, it has to be administered by frequent intramuscular injection or by continuous intravenous drip.

The low toxicity and the effectiveness against both gram-negative and gram-positive bacteria suggest that streptomycin will prove a valuable chemotherapeutic agent.

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**Observations on the Function of the Lymphocyte.** W. E. EHRLICH and T. N. HARRIS (Depts. of Pathology and Pediatrics, Univ. of Penna. and Phila. Gen. Hosp.). In a previous study of a limited and well-circumscribed system which included the hind foot of the rabbit (the site of injection), the lymph contained in the afferent lymph vessels, the popliteal lymph node (the only regional node to the site of injection), the efferent lymph, and finally the serum, it was shown that antibodies first appeared in the efferent lymph 2 to 4 days after injection of the antigen (typhoid bacilli, sheep erythrocytes) and reached their highest titer after 6 days. This antibody formation was preceded and accompanied by a marked rise in the output of lymphocytes in the efferent lymph and by hyperplasia of the lymphatic tissue within the lymph node. The fact that the cellular response was chiefly lymphocytic suggested that the lymphocyte may play an important rôle in antibody formation.

The present work rests upon the study of an even smaller and more isolated system, namely, the lymphocytes and the lymph plasma of the efferent lymph collected during the period of antibody formation. A comparison of the concentrations of antibodies contained in these two fractions revealed that 5 days after injection of the antigen the lymphocytes contained 8 or 16 times as much antibody as the lymph plasma. This observation offered only two possible interpretations, namely, that the lymphocyte either absorbs or adsorbs, or produces, antibodies. Normal lymphocytes were incubated with antibody-containing lymph plasma, as antibody-containing serum was injected into the living lymph node and lymph removed several hours later. In no case was it possible to show adsorption or absorption of antibodies by the lymphocyte. On the other hand, it was observed that the ratio between lymphocyte titer and lymph plasma titer was greatest on the 5th day when antibody formation was greatest, while 2 days later the ratio had dropped considerably. These findings seem to show that the lymphocyte produces, rather than absorbs or adsorbs, antibodies.

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**Carbon Monoxide Polycythemia.** HEINRICH BRIEGER (Division of Industrial Hygiene, Hahnemann Medical College and Hospital). A series of experiments on dogs and men furnished additional information on polycythemia in acute and in chronic carbon monoxide intoxication. I. *Acute CO Intoxication.* Polycythemia occurred, though not invariably. On the contrary, even decrease of Hb and RBC was encountered in our animal experiments. Hb values and RBC did not indicate a noticeable effect of early spleen contraction on the circulating blood.

Significant polycythemia was a late effect of high blood saturation with CO. Its full development could be observed several days after the exposure long after all CO had disappeared from the blood. Reticulocytosis and appearance of normoblasts indicated a stimulation of the bone marrow. Permanent polycythemia developed in 1 dog.



The correlation coefficient between Hb and RBC was, as a rule, not significant. II. *Chronic CO Intoxication*. Dogs were exposed for 11 weeks to an air concentration of 0.0096 vol. % CO leading to a blood saturation of 20.1 % COHb. Exposure for 9 weeks increased the RBC significantly; Hb showed a definite trend toward a similar increase. The values decreased during continued exposure to and slightly below the original level respectively. In the 3 months following the exposure, Hb rose in several dogs; in 1 animal to a level suggesting polycythemia.

Onset, development, and degree of the polycythemia varied considerably in the individual dogs. Polycythemia did not prevent the noxious effects on the circulatory and nervous systems in either acute or chronic CO intoxication.

# BOOK REVIEWS AND NOTICES

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**THE BABY MANUAL.** A Practical Guide from Early Pregnancy Through the Second Year of Life. By HERMAN N. BUNDESEN, M.D. Foreword by THOMAS PARRAN, M.D., Surgeon-General, U. S. P. H. S. Pp. 590; 137 figs. New York: Simon & Schuster, 1944. Price, \$3.00.

HERE is another baby-raising book, thicker than most. It displays a laudatory preface signed by the Surgeon-General of the U. S. P. H. S. and a note on the last page modestly crediting Dr. Bundesen with cutting Chicago's infant death rate in half. The contents consist essentially of an expansion of the controversial pamphlets distributed monthly by the Chicago Health Department, already published in parts in "Our Babies." The first half is expository, in simple narrative style; the second half asks and gives answers to some 1001 caretaking questions which may puzzle untutored mothers. In internal arrangement one finds "books" on (1) Prenatal Care; (2) Care of the Baby; (3) The Premature Baby; and (4) The First Two Years. By and large, the contained information is clear and in accord with modern practices. The discussion on how to promote the flow of breast milk is especially good. The many illustrations, all photographic, have been carefully planned to emphasize the points being made, though the one on page 85 is incorrect, for the infant's stomach 3 hours after a feeding is empty and contracted, or nearly so, not hyperdistended with air like a small blimp. The major fault of the book is that it says too much. In countless places the Author steps beyond the proper realm of pediatric nursing into the provinces—dangerous for parents—of diagnosis, treatment and formula-writing. He offers specific instructions on feeding regulation, including when to wean, how to construct infant feeding mixtures according to body weight and age in months, when, which, and what dosage of vitamins to feed. He directs parents how to diagnose and prescribe for such diseases as boils, scabies, head lice, impetigo, middle ear infection, diarrhea, mumps, and chickenpox. Though the text is liberally sprinkled with statements counseling that "the doctor" be consulted about this or that difficulty, the selfsame paragraphs usually give explicit advice regarding the complaints in question. One can see that many a penny-wise and cocksure layman will lean upon this book with its generalizations in place of taking his child to a pediatrician or family physician for periodic examinations and individualized guidance. Amateur learning can be highly dangerous, especially for baby health. The justification given by both Dr. Bundesen and Dr. Parran is the shortage of civil practitioners during these war years. But the military emergency is temporary, whereas the book will go on and on, especially if it sells well, and defects minimized now will assume normal stature soon again. Therefore, though this book would prove helpful to graduate nurses active in infant welfare, to medical students working in pediatric dispensaries and to isolated missionaries and ranchers wanting to rear their families by modern methods, it is not likely that doctors who see infants at monthly intervals will welcome such an ill-planned body of information being placed in parents' hands.

I. W.

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**HIPERTENSION ARTERIAL NEFROGENA.** By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCILO, LUIS F. LELOIR, JUAN M. MUNOZ, and ALBERTO C. TAQUINI, Instituto de Fisiologia de la Facultad de Ciencias Medicas de Buenos Aires; Instituto de cardiologia Fundacion V. F. Grego. Pp. 462; 93 figs. Buenos Aires: Liberia y Editorial "El Ateneo," 1943.

For those interested in reviewing the investigative work on hypertension reported during the past decade, this book will serve as an excellent guide.

It emphasizes the point of view of the Authors who, with B. A. Houssay, have performed numerous experiments along the same lines as those done by Page and his associates in this country. The first 3 chapters deal with the various methods of producing experimental hypertension and the pathology, pathogenesis, and abnormal physiology of animals so affected. Then follow discussions of renin, hypertensinogen and hypertensin. Finally, there are adequate discussions of the relationships between experimental hypertension and essential hypertension in man, and of the medical and surgical aspects of the treatment of hypertension. The bibliography refers to 1104 papers, drawn chiefly from the American literature.

W. J.

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A SOURCE-BOOK OF BIOLOGICAL NAMES AND TERMS. By EDMUND C. JAEGER, Riverside Junior Coll., Riverside, Calif. Pp. 256. Springfield, Ill.: Charles C Thomas, 1944. Price, \$3.50.

To those who are interested in the structure of biologic terms for etymologic or semantic reasons, and to those who find the literal meaning of a word useful in comprehending and teaching new knowledge, this book will be satisfying and instructive. "Students of medicine and dentistry, veterinarians, foresters, ranger-naturalists, quarantine officers, crop inspectors, paleontologists, physiologists, entomologists, biologists, botanists, zoölogists, mycologists, technical workers in special scientific fields, and laymen who have as a hobby a scientific subject, will find it a book constantly useful. . . . Teachers of Latin and Greek interested in teaching the derivation of words useful to science students will find here a veritable storehouse of useful information. Scientists will find it a ready and rich source of word elements useful in coining new names."

The opening pages, which should be read carefully by those intending to use the book, give insight into the philosophy of word building. One sees, for instance, how the same root may enter into a number of compound words with different, yet correct, endings (*e. g.*, 16 different yet correct combinations of *kalos* and *mus* [beautiful mouse] are offered from actual usage). The book also helps toward better spelling and pronunciation of scientific tongue-twisters.

Though thousands of word elements are presented, yet they were carefully chosen and offered as merely illustrative; also, as it is a source-book, definitions are not included. For each word or stem, the derivation and examples are given, literally interspersed with space-saving symbols. One should not be surprised at the great frequency of insect species and genera.

E. K.

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POISONOUS PLANTS OF HAWAII. By HARRY L. ARNOLD, M.D., F.A.C.P., Chief of Medical Service, The Queens Hosp., Honolulu. Pp. 71; 24 full-page illus. Honolulu, Hawaii: Tongg Publishing Co., 1944.

THIS privately printed booklet—the outgrowth of an earlier article that is now out of print—presents first the common and dangerous plants known to have caused serious poisoning; and then a larger number of plants listed by various authors as dangerous. The numerous full-page illustrations should be helpful in identification.

This should be a valuable book for the inhabitants of Hawaii, and for sojourners there.

E. K.

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TEXTBOOK OF REHABILITATION, RE-EDUCATION AND REMEDIAL EXERCISES. By OLIVE F. GUTHRIE SMITH, M.B.E., C.S.M.M.G., T.M.G., Principal of the Swedish Inst., London, Director of the Physical Exercise Depart. of St. Mary's Hosp., Member of the Council of the Chartered Society of Physiotherapists. Foreword by LORD HORDER, G.C.V.O., M.D., F.R.C.P. Pp. 424; 273 figs. Baltimore: Williams & Wilkins, 1943. Price, \$6.00.

THIS book follows the current trend of adding more strenuous exercises to the older, conservative procedures of physiotherapy. It is of particular

interest at present when there is emphasis upon the rehabilitation and reconditioning of soldiers. Information is presented in a manner which is at once clear and concise, yet in sufficient detail to be easily understood and put into practice.

The book covers 3 principal topics, as the title indicates. Following a discussion of rehabilitation, the Author describes the more strenuous exercises, and leaves the subject of passive treatments for the final chapters. The part played by suspension therapy is well illustrated. A. R.

THE MEDICAL CLINICS OF NORTH AMERICA. New York Number. SYMPOSIUM ON PSYCHOSOMATIC MEDICINE. By 18 Contributors. Pp. 787; 62 figs. Philadelphia and London: W. B. Saunders, 1944.

THIS New York number, a symposium on Psychosomatic Medicine, includes in its list of contributors: Dr. Leland E. Hinsie, Dr. Rene A. Spitz, Dr. Nolan Lewis, Comdr. A. M. Master, U.S.N.R., Dr. Asher Winkelstein, Dr. George E. Daniels, Dr. J. Louise Despert, Drs. James S. Greene and S. Mouchly Small, Drs. John Romano and George L. Engle, Dr. Milton Erickson, Dr. Flanders Dunbar, Dr. John J. Moorhead, and Dr. Alvan L. Barach.

The volume also contains additional clinics on "Symptoms Referable to Digestive Organs Resulting from Diseases of Abdominal Blood Vessels" by Dr. I. W. Held; "Medical Ophthalmologic Aids and Practice" by Dr. Ferdinand L. P. Koch; "Rocky Mountain Spotted Fever" by Dr. George E. Baker.

In addition to the diversity of subjects touched in the Symposium on Psychosomatic Medicine, the general reader has at his command a storehouse for ready reference in psychosomatic field. For the most part, for a general audience the participants have expressed themselves in a neatly understood fashion. H. B.

GLOBAL EPIDEMIOLOGY, A Geography of Disease and Sanitation. By JAMES STEVENS SIMMONS, B.S., M.D., Ph.D., DR.P.H., Sc.D. (Hon.), Brigadier General, U.S.A., Chief Preventive Medicine Service, Office of the Surgeon-General, U.S.A.; TOM F. WHAYNE, A.B., M.D., Lieut. Col., M.C., A.U.S., Formerly Director, Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General, U.S.A.; GAYLORD WEST ANDERSON, A.B., M.D., DR.P.H., Lieut. Col., M.C., A.U.S., Director, Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General, U.S.A., Director, School of Public Health, University of Minnesota; HAROLD MACLACHLAN HORACK, B.S., M.D., Major, M.C., A.U.S., Chief Dissemination Branch, Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General, U.S.A.; Instructor in Medicine, Duke University School of Medicine; and Collaborators. Vol. 1, Part 1: India and the Far East; Part 2: The Pacific Area. Pp. 504. Philadelphia: J. B. Lippincott, 1944. Price, \$7.00.

THERE is a definite need for a study of this type, due to the fact that men of our armed forces are stationed throughout the world, and are constantly returning to this country. We are presented with Volume One which covers India, the Far East, and the Pacific area. Other volumes will undoubtedly follow.

This book is a compilation of studies drawn up much in the fashion of the War Department Technical Bulletins which have appeared on the medical and sanitary data of the various countries and islands. These bulletins and the material of this book were based on the studies made by the Medical Intelligence Division, Preventive Medicine Service, Office of the Surgeon-General. Each country and island is taken up in turn with a discussion of the geography and climate, public health service, water supply, sewage disposal, vectors of disease, food and dairy products, problems of sanitation, hospital and medical facilities, and disease incidence.

This work will be chiefly of value as a reference volume. It will be useful to those treating our returning soldiers and to those pioneers of industry who may already be planning reconstruction or the opening up of new industries in the Far East.

The book is well presented with frequent small diagrams showing occurrence of disease within the various localities. Each section is complete with bibliography.

D. P.

**DISEASES OF THE DIGESTIVE SYSTEM.** Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., Associate Professor of Medicine, University of Illinois Med. School (Rush); Attending Physician, Michael Reese Hosp.; Consulting Physician, Cook County Hosp.; Consultant in Medicine to the Inst. of Psychoanalysis, Chicago. Second Ed. Pp. 932; 182 illus. Philadelphia: Lea & Febiger, 1944. Price, \$11.00.

THIS second edition of the first comprehensive textbook in English on the diseases of the entire digestive system will be welcomed by teachers, practitioners and students. The first edition met a distinct need, but recent progress in the field necessitated more than a revision. Even now certain sections, such as that on epidemic hepatitis, need revision and elaboration. No textbook, however, can be entirely up to date. The chief merits of this one are its all-inclusiveness, the emphasis which has been placed on the functional aspects of gastro-enterology and the relationship of digestive disturbances to disease in other systems of the body. The 50 contributors are well known in connection with the subjects they discuss and their names add weight to the opinions expressed. An ample bibliography accompanies each chapter, the illustrations are excellent, and the general arrangement of the subject matter enhances its value for reference.

M. H.

**CATARACT AND ANOMALIES OF THE LENS.** Growth, Structure, Composition, Metabolism, Disorders, and Treatment of the Crystalline Lens. By JOHN G. BELLOW, M.D., Ph.D., Assistant Professor of Ophthalmology, Northwestern Univ. Med. School, Chicago. Pp. 624; 208 figs.; 4 color plates. St. Louis: C. V. Mosby, 1944. Price, \$12.00.

THE material in this book includes everything of importance that is known today about the animal and human lens. Almost all of this material could be found elsewhere either in textbooks or in ophthalmologic literature; but the Author brings together here in one volume a great deal of information of reference value heretofore scattered in many volumes, probably the chief contribution made by this publication. Not the least of this material is that which is derived from the Author's own researches in recent years, particularly on the chemistry and metabolism of the lens and on experimental cataracts. The accompanying bibliography is extensive. The volume is not essential to all, but is a valuable addition to any well-rounded ophthalmologic library.

F. A.

**RECENT ADVANCES IN ANÆSTHESIA AND ANALGESIA** (Including Oxygen Therapy). By C. LANGTON HEWER, M.B., B.S. (LOND.), D.A. (ENG.). Fifth ed. Pp. 343; 141 figs. Philadelphia: Blakiston, 1944. Price, \$5.50.

THIS fifth edition of a popular, compact handbook, written by an authoritative British worker, primarily reflects the English point of view. As a consequence, certain characteristics are evident. Description of apparatus is more of local than of general interest. The references are largely European; and, finally, current ideas are those of the British group. The advantages of this type of presentation in broadening an American's knowledge are obvious. Some new material has been added since the 1943 edition, but this is not striking.

R. D.

**THE URINARY TRACT.** A Handbook of Roentgen Diagnosis. By H. DABNEY KERR, M.D., Professor of Radiology, State Univ. of Iowa Coll. of Medicine, and CARL L. GILLIES, M.D., Associate Professor of Radiology, State Univ. of Iowa Coll. of Medicine. Pp. 320; numerous figs. Chicago: Year Book Publishers, 1944. Price, \$5.50.

THIS volume fills a long existing need for a concise, informative reference on the use of the Roentgen ray in urologic diagnosis. The clinical material was gathered from the records of the University of Iowa Hospital. Illustrations are well selected and excellently reproduced.

The book is divided into 4 major sections: the kidney, ureter, bladder, and urethra. Under each of these sections the normal roentgenologic appearance of the organ is given. All practical methods of study are used. Because no 2 lesions, or normal structures, are alike, the authors show several examples of every condition wherever possible. Following illustrations of the normal appearances of the organs are those of all common abnormal conditions, such as stone, tumor, non-specific infection, tuberculous infection, congenital anomalies, and traumatic lesions. Many illustrations of uncommon lesions are also given.

Adequate radiographic study is an important factor in diagnosis of urologic disease. One cannot study this book without realizing this fact. However the Authors emphasize the fact that in determining the status of the urinary tract it is necessary to correlate all clinical and laboratory data with the Roentgen findings before making a final diagnosis.

As a text and as a reference, this book should be of value to students, practitioners, and specialists.

L. La T.

**X-RAY EXAMINATION OF THE STOMACH.** A Description of the Roentgenologic Anatomy, Physiology, and Pathology of the Esophagus, Stomach, and Duodenum. By FREDERIC E. TEMPLETON, M.D., Head of the Dept. of Roentgenology, The Cleveland Clinic; Formerly Associate Professor of Roentgenology at the Univ. of Chicago. Pp. 516; 297 figs. Chicago: Univ. of Chicago Press, 1944. Price, \$10.00.

THIS book contains 18 chapters on the Roentgen examination of the pharynx, esophagus, stomach and duodenum. It considers all of the various details concerned with those examinations, including the apparatus, the media, the technique of the examination and the basic principles of interpretation. It also includes the anatomy, physiology, and pathology of the various structures. The title is unfortunate in that it does not convey to the reader the content of the text. The subtitle is much more accurate.

The Author has considered in an erudite manner all phases of the Roentgen examination of the pharynx, esophagus, stomach and duodenum, drawing on both his own experience and many excellent articles on this subject. His consideration of the anatomy and physiology of the part, as determined experimentally by the Roentgen examination and by other methods, makes the book well worth reading. It will be most useful not only to the inexperienced radiologist but to the more experienced radiologist and teachers in anatomy, physiology, and radiology.

The paper used by the publisher is good; the illustrations are excellent, and for the most part the format of the book is satisfactory. There are some features in the format of the book that are not conventional and one suspects that the shortage of paper may be the explanation. The Reviewer refers to the fact that Chapter 1 includes the Introduction and on page 3 the first chapter is finished and it immediately starts into Chapter 2—The Apparatus.

The Reviewer was much surprised to see such a poor index for such an excellent text. It does not in any way convey what there is in the text. If properly indexed, this book would take many more pages.

Likewise, the Reviewer was somewhat surprised to see the improper use of roentgenologic terms. For instance, frequently the word film is used where the Author is referring to a roentgenogram. Likewise, the word x-ray is used

where the Author refers to the Roentgen examination or the x-ray examination. These criticisms are minor. The book is an excellent contribution and will serve a most useful purpose.

E. P.

**MEDICAL CLINICS OF NORTH AMERICA.** The Mayo Clinic Number. SYMPOSIUM ON CHEMOTHERAPY. By 36 Contributors. Pp. 789-1028; 75 figs. Philadelphia and London: Saunders, 1944. Price, \$16.00 per year.

THIS edition contains 2 parts: the first covers the clinical usages of the sulfonamides in general medicine and the specialties; the second consists of numerous articles on miscellaneous subjects of both medicine and surgery as covered by specialists at the Mayo Foundation.

Common problems encountered in the course of treatment are covered, both with the older sulfonamides and the newer drugs, including sulfamerazine, sulfamethazine and sulfasuxidine. A broad field of treatment is opened to the general practitioner through the clinics given on the sulfonamides in the specialties—ophthalmology, otolaryngology, urology and pediatrics.

The second part contains a number of articles, both interesting and useful with respect to keeping a busy doctor abreast of recent developments. Of special appeal are the articles on the peripheral blood count and the clinic occurrence of eosinophilia.

J. W.

**ANNUAL REVIEW OF BIOCHEMISTRY.** By JAMES MURRAY LUCK, Editor, Stanford Univ., and JAMES H. C. SMITH, Associate Editor, Carnegie Inst. of Washington, Division of Plant Biology, Stanford Univ., California. Vol. 13. Pp. 795. California: Stanford Univ. P. O., Annual Reviews, Inc., 1944. Price, \$5.00.

THE 1944 edition follows the same general plan as the previous volumes, and for the most part the same subjects are covered, including oxidations and reductions, enzymes, chemistry and metabolism of carbohydrates, fats and proteins, nutrition, and so on. As usual, there are a few subjects in this volume which have either been reviewed at infrequent intervals or are making their appearance for the first time. Among these may be mentioned the chapter on The Nutritional Deficiencies in Farm Animals on Natural Feeds, by C. F. Huffman and C. W. Duncan; a chapter on Photoperiodism in Plants, by K. C. Hammer; one on Chloroplast Pigments, by H. H. Strain, and one on Histochemistry, by D. Glick. The reviewers of these last-named subjects have not confined themselves to the most recent literature but have presented their subjects more in the form of general reviews.

Like the other volumes of this series there is a surprising absence of typographical errors, and in every other respect this volume meets the high standard set by the previous numbers.

J. J.

**TABER'S DICTIONARY OF GYNECOLOGY AND OBSTETRICS.** By CLARENCE WILBUR TABER, Medical Editor and Author of Taber's Cyclopedic Medical Dictionary, Taber's Condensed Medical Dictionary, and Dictionary of Food and Nutrition, etc. With the Collaboration of MARIO A. CASTALLO, M.D., F.A.C.S., Assistant Professor of Obstetrics, Jefferson Med. Coll.; Gynecologist to St. Mary's and St. Agnes' Hosps.; Obstetrician to St. Mary's Hosp.; Diplomate, American Board of Obstetrics and Gynecology, etc. Pp. 706; numerous illus. Philadelphia: F. A. Davis, 1944. Price, \$3.50.

DEFINITIONS are of fundamental importance in any subject; but are of special value to students, teachers and writers. Therefore, Taber's Dictionary is most welcome, especially to those who teach in the fields of gynecology and obstetrics. This volume, although it is built around definitions, is more than a mere dictionary. Many of the subjects which it lists are much more fully treated than is the case with the usual dictionary. In addition, it contains a number of useful illustrations. In my opinion, it should be in every library dealing with the subjects it covers.

D. M.

THE MEDICAL CLINICS OF NORTH AMERICA. SYMPOSIUM ON SPECIFIC METHODS OF TREATMENT. The Boston Number. 22 Contributors. Pp. 1292; 96 figs. Philadelphia & London: Saunders, 1944. Price, \$16.00 a yr.

THIS number is made up of a series of discussions on the management of certain outstanding medical and psychomatic problems. The articles are clearly written and several contain charts useful in summarizing the material presented. Penicillin and thiouracil, as newer therapeutic agents, are included; also, by Stanley Cobb, a technique for interviewing a patient with a psychomatic disorder. Chester M. Jones discusses the functional gastro-intestinal disturbances, and Edward C. Reifenstein presents a very helpful and practical paper on endocrinology. Three articles on pediatrics (acute bronchiolitis, adenoid bronchitis and chronic diarrhea) are included. The treatment of diseases of the heart and of the kidney is covered, respectively, by Paul D. White and George W. Thorn. Altogether this is a very readable and useful book.

M. H.

OUR AMERICAN BABIES. The Art of Baby Care. By DOROTHY V. WHIPPLE, M.D. Introduction by C. ANDERSON ALDRICH, M.D., Chief of Staff, The Children's Memorial Hosp., Chicago. Pp. 367; numerous figs. and tables. New York: M. Barrows, 1944. Price, \$2.50.

THIS new guide to baby care is one of the finest to appear in recent years. It is clear, direct, readable, and packed with homespun counsel of the most practical sort. Dr. Whipple has 3 children of her own (whose faces presumably appear in some of the colorful photographs which contribute so much to the appeal of the book), and she writes from experience gained both as a pediatrician and as a mother. There are 6 sections: Preparing for the First Baby; As the Baby Grows; Food and Feeding; Keeping the Baby Well and Happy; Prevention and Treatment of Disease in Babies and Young Children; The Baby's Grownups. Advice and instruction are given not only on such exclusively bodily matters as breast feedings, cuts and wounds, the fitting of shoes, and enema-giving—to cite but a few instances—but on more domestic problems such as buttons *versus* ties on baby garments, metal *versus* glass drinking cups, companionship with the father, birthday parties, and "the art of being a grandmother."

I. W.

COLORIMETRIC DETERMINATION OF TRACES OF METALS. By E. B. SANDELL, PH.D., Assistant Professor of Analytical Chemistry, Univ. of Minnesota. Vol. 3. Pp. 487; 73 figs.; 66 tables. New York: Interscience Publishers, 1944. Price, \$7.00.

THIS excellent monograph is the third volume of a current series upon Chemical Analysis. In it Dr. Sandell presents clearly a great many sensitive chemical methods which have been devised for the determination of trace metals. The work happily meets a real need for a collection under one cover of information which heretofore has been most difficult to find without arduous search through scattered original literature.

Trace metals are of great importance not only in industry, as for example in the analysis for impurities in steel, but also in biology. The list of trace metals of interest to the biologist concerned with metabolism or pathology is constantly growing. Such a list includes iron, copper, zinc, manganese, aluminum, cobalt, nickel, lead, arsenic, bismuth, and mercury. It is gratifying that the Author has included, for all the above, techniques adapted to biologic material.

Preliminary chapters are devoted to general procedures such as adsorption and to the methods of colorimetry (photometry), spectrophotometry, and fluorimetry. This material is presented briefly, and perhaps somewhat sketchily. On the whole, however, the book is a more than adequate summary of the field which it covers and is highly recommended by the Reviewer.

D. D.



**EXPERIMENTAL SPECTROSCOPY.** By RALPH A. SAWYER, PH.D., Professor of Physics, Univ. of Michigan; now Lt. Comdr., U.S.N.R., and on leave from the Univ. of Michigan. Pp. 323; 107 figs. New York: Prentice-Hall, 1944. Price, \$6.00.

THE review of a book upon spectroscopic techniques would have appeared out of place in a medical journal some years ago. That such a review is presented at this time is an indication of the ever-increasing overlapping of the various branches of science. The Author has produced a short text, crammed full of facts, based largely on his own extensive experience. The book is clearly written and very readable. The lucidity of presentation probably accounts for its small size. All technical matters of importance are dealt with adequately. It is to be regretted that only a very brief chapter is devoted to spectrochemical analysis, a field in which Commander Sawyer has been personally concerned. It is to be hoped, also, that in a revision of this work more space may be devoted to absorption spectrophotometry, at present of greater primary interest to biologists than line spectra. The Reviewer believes that this excellent book may well become a standard work in its field.

D. D.

**ALL ABOUT FEEDING CHILDREN.** By MILTON J. E. SENN, M.D., Associate Attending Pediatrician, New York Hosp.; Associate Professor of Pediatrics in Psychiatry, Cornell Univ. Med. Coll.; and PHYLLIS KRAFFT NEWELL. Pp. 269. New York: Doubleday, Doran & Co., 1944. Price, \$2.50.

THIS manual, produced by the joint collaboration of a skilled dietitian and a pediatrician specializing in child psychiatry, discusses the myriad facets of the feeding of normal children. The best picture of the content is given by the list of chapter headings: "Good Nutrition Is Every Child's Birthright; Establishing the Young Infant's Feeding Schedule; The Breast-Fed Baby; The Bottle-Fed Baby; Preparing Special Formulas; Some Feeding Facts That Grandma Didn't Know; Dysfunctions Associated With Eating; Foods for Your Baby's First Year; Feeding the Child Between 1 and 2 Years old; Feeding the Child Between 2 and 6 Years Old; Feeding Children Between 6 and 12 Years Old; Eating With the Family; Equipment for Preparing Your Child's Food; Water; Cod-Liver Oil and Other Vitamin-D Sources; Cereals, Breadstuffs, and Macaroni Products; Eggs; Vegetables; Fruits; Meat, Fish, and Poultry; Soups; Sweets and Desserts; Fats; Salads and Salad Dressings; Milk and Milk Products in the Diet of Older Children; Beverages; Special Diets and Foods Your Physician May Order; Parties, Picnics, and Holidays; The School Lunch Box; Traveling With Young Children; Food and the War." The recipes and instructions for the choice and preparation of foods supplement nicely the dissertations on the psychologic aspects of the giving and eating of the foods.

This book will appeal equally to mothers, to school dietitians and to physicians whose practices include children. It is well planned, thorough, readable, and excellent in all respects.

I. W.

## NEW BOOKS

**Trichinosis.** By SYLVESTER E. GOULD, M.D., D.Sc., Pathologist and Director of Laboratories, Eloise Hosp., Eloise, Mich.; Assistant Professor of Pathology, Wayne Univ. Coll. of Med., Detroit. Pp. 356; 128 figs. Illinois: Thomas, 1945. Price, \$5.00.

**A Bibliography of Aviation Medicine.** Supplement. By PHEBE MARGARET HOFF, EBBE CURTIS HOFF, and JOHN FARQUHAR FULTON. Publication No. 9, Historical Library, Yale Medical Library. Pp. 109. Illinois: Thomas, 1944. Price, \$2.50.

**The Biological Basis of Individuality.** By LEO LOEB, Professor Emeritus of Pathology, Washington Univ. School of Med., St. Louis. Pp. 711. Illinois: Thomas, 1945. Price, \$10.50.

- The Experiments of Nature and Other Essays.* By IRVINE McQUARRIE, Ph.D., M.D., Dept. of Pediatrics, The Medical School, Univ. of Minnesota, Minneapolis, Minn. Delivered at the Univ. of Kansas School of Med., Lawrence, Kansas City. Porter Lectures, Series 12. Pp. 115; 16 figs. Kansas: Univ. of Kansas, Univ. Extension Division, 1944.
- Crime and the Human Mind.* By DAVID ABRAHAMSEN, M.D., Dept. of Psychiatry, Columbia Univ. Pp. 244. New York: Columbia Univ. Press, 1944. Price, \$3.00.
- Medical Clinics of North America.* Philadelphia Number. Symposium on Recent Advances in Medicine. Pp. 1293 to 1608. Index for 1942-1944. Philadelphia and London: Saunders, 1944. Price, \$16 per year.
- Control of Pain in Childbirth.* By CLIFFORD B. LULL, M.D., F.A.C.S., Clinical Professor of Obstetrics, Jefferson Med. Coll.; Assistant Director, Phila. Lying-In Unit, Penna. Hosp.; and ROBERT A. HINGSON, M.D., Surgeon, U. S. Public Health Service; Director, Post-graduate Medical Course, Phila. Lying-In Unit, Penna. Hosp. With an introduction by NORRIS W. VAUX, M.D., Obstetrician-in-Chief, Phila. Lying-In Unit, Penna. Hosp. Pp. 356; 100 illus., 32 subjects in color. Philadelphia: Lippincott, 1944. Price, \$7.50.
- The Art of Resuscitation.* By PALUEL J. FLAGG, M.D., Chairman, Comm. on Asphyxia, Am. Med. Assn.; President and Founder of the Soc. for the Prevention of Asphyxial Death, Inc.; Director of Pneumatology, New York World's Fair, 1939, Inc.; Author, "Art of Anæsthesia"; Visiting Anesthetist, Manhattan Eye and Ear Hosp.; Consulting Anesthetist to St. Vincent's Hosp., The Woman's Hosp., Sea View Hosp., Jamaica Hosp., Mount Vernon Hosp., Flushing Hosp., Mary Immaculate Hosp., St. Mary's Hosp. and Nassau Hosp. Pp. 453; 176 figs. New York: Reinhold, 1944. Price, \$5.00.
- Outline of the Amino Acids and Proteins.* Edited by MELVILLE SAHYUN, M.A., Ph.D., Vice-President and Director of Research, Frederick Stearns & Co., Detroit, Mich. Contributing Authors: HENRY B. BULL, WILLIAM M. CAHILL, HERBERT E. CARTER, DAVID M. GREENBERG, MICHAEL HEIDELBERGER, IRVING R. HOOPER, CARL L. A. SCHMIDT, C. F. KADE, ARMAND J. QUICK, MELVILLE SAHYUN, ARTHUR H. SMITH, MADELYN WOMACK, DEAN LAURENCE. Pp. 251. New York: Reinhold, 1944. Price, \$4.00.
- Laboratory and Clinical Studies.* Vol. XXIV. From the Memorial Hosp. for the Treatment of Cancer and Allied Diseases. Forty-one Contributors. New York, 1943.
- Large Scale Rorschach Techniques.* A Manual for the Group Rorschach and Multiple Choice Test. By M. R. HARROWER-ERICKSON, ACAD. DIP., Ph.D., Research Associate, Dept. of Neuropsychiatry, Univ. of Wisconsin; and M. E. STEINER, B.A., M.A., Personnel Section, General Electric Co., Bridgeport, Conn. Pp. 420; 47 tables; 70 illus. Illinois: Thomas, 1945. Price, \$8.50.
- Handbook of Industrial Psychology.* By DR. MAY SMITH. Pp. 304. New York: Philosophical Library, 1944. Price, \$5.00.
- Soldier to Civilian.* Problems of Readjustment. By GEORGE K. PRATT, M.D., Psychiatric Examiner, U. S. Armed Forces, Induction Center, New Haven, Conn.; Formerly Assistant Clinical Professor of Psychiatry, School of Med., Yale Univ. Foreword by GEORGE S. STEVENSON, M.D., Medical Director, The National Committee for Mental Hygiene. Pp. 231. New York and London: Whittlesey House, McGraw-Hill, 1944. Price, \$2.50.

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#### NEW EDITIONS

- Foundations of Neuro-psychiatry.* By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Med. School; Psychiatrist in Chief, Massachusetts General Hosp. Third ed. Pp. 252; numerous figs. Baltimore: Williams & Wilkins, 1944. Price, \$2.50.

*Elements of Electrocardiographic Interpretation.* By LOUIS N. KATZ, A.M., M.D., Director of Cardiovascular Research, The Michael Reese Hosp., Chicago; Professorial Lecturer in Physiology, The Univ. of Chicago; and VICTOR JOHNSON, Ph.D., M.D., Professorial Lecturer in Physiology, The Univ. of Chicago. Third ed. Pp. 44; 40 plates illustrating the more important deviations from the normal, selected from the files of the Michael Reese Hospital. Illinois: The Univ. of Chicago Press, 1944. Price, \$1.00.

*Clinical Practice in Infectious Diseases.* For Students, Practitioners and Medical Officers. By E. H. R. HARRIES, M.D. (LOND.), F.R.C.P., D.P.H., Medical Supt., North-Eastern Hosp. (London County Council); Formerly Med. Supt., City Hosp., and Univ. Clinical Lecturer in Fevers, Birmingham; Milroy Lecturer, Royal Coll. of Physicians, London; and M. MITMAN, M.D. (LOND.), M.R.C.P., D.P.H., D.M.R.E., Med. Supt., River Hosps.; Formerly Med. Supt., Eastern Hosp., and Divisional Medical Officer, Public Health Dept., London County Council. With a Foreword by W. ALLEN DALEY, M.D. (LOND.), F.R.C.P., D.P.H., Medical Officer of Health, London County Council. Second ed. Pp. 570; 26 tables; 52 figs. Edinburgh: E. & S. Livingstone, 1944. Price, \$6.00.

*Arthritis and Allied Conditions.* By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Associate in Medicine, Univ. of Penna.; Senior Ward Physician and Chief of the Arthritis Clinic Hosp. of the Univ. of Penna. Third ed., enlarged and thoroughly revised. Pp. 1359; 329 illus. Philadelphia: Lea & Febiger, 1944. Price, \$12.00.

*Symptoms of Visceral Disease.* A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.F., Medical Director, Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, Calif.; Professor Emeritus of Clinical Medicine, Univ. of Southern California; Author of "Clinical Tuberculosis," "Tuberculin in Diagnosis and Treatment," "Muscle Spasm and Degeneration," etc. Sixth ed. Pp. 442; 87 illus. and 10 color plates. St. Louis: Mosby, 1944. Price, \$5.00.

*Contagious Diseases.* A Guide for Parents. By W. W. BAUER, B.S., M.D., Director, Bureau of Health Education, Am. Med. Assn.; Associate Editor, *Hygeia, The Health Magazine*; Formerly Epidemiologist, Milwaukee Health Dept.; Lecturer in Public Health, Marquette Univ. Commissioner of Health, Racine, Wis. Second ed. Pp. 188. New York: Knopf, 1944. Price, \$2.00.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1945

## ORIGINAL ARTICLES

### FILARIASIS IN SOLDIERS ON AN ISLAND IN THE SOUTH PACIFIC

BY CAPT. THEODORE D. ENGLEHORN, M.C., A.U.S.

AND

LIEUT. WILLIAM E. WELLMAN, M.C., A.U.S.

WALLA WALLA, WASH.

FILARIASIS has been known to exist on the islands of the eastern part of the South Pacific Ocean for many years. Several investigations have been carried out among the natives of these islands, as a result of which the infection is attributed to *Wuchereria bancrofti*. The life cycle of the parasite and its transmission by the mosquito are well known and will not be described in this article.

The Authors were attached to a small field hospital accompanying a task force. The personnel included no one specially trained in tropical medicine. For some months the outfit was incompletely equipped to study or to attempt the control of the disease to be described. From the information supplied by medical officers who had arrived in this area earlier, and from observations among the natives, which are described later, we soon became aware of the possibility that filariasis might appear among the troops under our care. A study of the literature available to us gave no clue as to the manner in which soldiers freshly infected would react to the disease. No information could be obtained as to how soon after the first exposure to the infection symptoms or signs should be expected.

The purpose of this article is to describe the clinical picture presented in the course of time by soldiers among the troops on the island. The account which is given here is specifically based on the study of 127 soldier patients. We believe, in common with many other medical officers with a similar experience, that this is the picture of early filariasis and that our observations furnish a basis for the clinical diagnosis of early filariasis, as will be described later. Seldom, if ever, has such an opportunity for the study of the beginning of this disease in freshly exposed adults previously offered itself. The opportunity also existed for comparison with a large group of natives who had had filariasis all their lives. A short account of the disease among natives, therefore, is included in the latter part of the article.

**Incubation Period.** A conclusive statement of the length of the incubation period cannot be made. The shortest time after first exposure in which any of our patients developed symptoms which were definitely attributed to filariasis was 3 months. Mild symptoms appeared in the majority of cases after 5 months' exposure, while more severe symptoms were seen, as a rule, after 8 months. In some cases, 14 months elapsed before the development of symptoms. It seems likely that the incubation period varies a good deal in length.

**Symptoms and Signs.** When the records of patients who developed characteristic signs were examined, it was found that most of these patients had complained of undiagnosable symptoms beforehand. In retrospect, it became apparent that many soldiers had reported to the dispensary with these early symptoms for some time before the possibility that they might be associated with filariasis was recognized. Common among these symptoms were anorexia, nausea and vomiting, and pains having a variable and remarkable distribution to the back, suprapubic region, groin, spermatic cord, testicles, and the inside of the thighs. The severity of these symptoms varied greatly, often being mild, but occasionally requiring hospitalization. Pain in the scrotum was sometimes described as being as great as if the patient had been kicked. In general, the more severe the early symptoms, the more marked were the later manifestations.

Further developments were found to occur, as a rule, from 10 to 14 days after the first symptoms. They consisted for the most part of involvement of the scrotal contents which occurred in 75% of our patients and of involvement of superficial lymph vessels and nodes of the arm or leg.

The first physical finding was often acute epididymitis with swelling and tenderness of the upper pole, which in time affected the whole organ. The most frequent abnormality was acute funiculitis. It was observed in some cases that epididymitis subsided when funiculitis developed; in other instances the two lesions coëxisted. There was usually marked tenderness over the inguinal canal, especially over the internal ring. Sometimes the swollen cord could be felt in the canal. Swelling of the cord where it emerges from the external ring was detectable early in the course. In size the swollen cord varied from 2 to 5 times its normal diameter. Varicoceles, usually lasting only a week or two, developed in some patients with funiculitis. In some instances there was an exacerbation of a chronic varicocele. No diagnostic weight was given to this particular development, because of its frequent occurrence in other circumstances. Tense swelling of the testicle to twice its usual size was a common finding. Hydrocele was not encountered in soldier patients, although it was found in many natives with late disease. Generalized scrotal swelling, with soft, boggy thickening of the wall appeared only after some weeks, usually in association with changes in the scrotal contents.

It was observed that pain often disappeared when the scrotal swelling became maximal. Many patients with these lesions suffered from severe malaise, cold sweats, nervousness and worry. Since all patients

had seen numerous cases of advanced elephantiasis among natives, the source of such nervousness was obvious.

Involvement of the superficial lymph nodes and vessels was much less frequent than that of the scrotal contents. When it occurred in these patients, it was associated with pain, tenderness, and swelling. In the arm, the axillary nodes were first affected, later the epitrochlear. A wide red streak which was raised, extremely tender, and could be felt as a cordlike structure, extended along the inner border from the axilla to the elbow. It was often over  $\frac{1}{2}$  inch in width. In some cases cellulitis developed, especially below the biceps muscle, which tended to become a burrowing abscess. Occasionally the lymphangitis proceeded down both sides of the forearm, even into the fingers which become swollen and painful. The same chain of events was observed in the thigh, beginning with the nodes of the groin and spreading down the medial side, but seldom going below the knee. In a few cases, however, the only finding was lymphangitis of the ankle and foot. In these instances, it seems probable that deep lymphatics higher up were involved. When cellulitis occurred in the thigh, it was usually confined to the upper inner third. Patients often complained strongly of pain on walking. The progress of lymphangitis was frequently observed and was always noted to proceed toward the periphery, both in the arm and in the leg.

The most important of these findings are listed in Table 1. They were seen in many different combinations. As the table indicates, for unknown reasons, involvement of the scrotal contents on the left side was much more frequent than on the right. The left arm and leg were more often affected than the right, but the number of cases here was small.

TABLE 1.—THE OCCURRENCE OF CERTAIN LESIONS IN 127 PATIENTS

Lesion	No. of patients		
	Left	Right	Total
Funiculitis . . . . .	95	32	127
Orchitis . . . . .	48	21	69
Epididymitis . . . . .	11	11	22
Lymphadenitis, acute . . . .	9	..	9
Lymphangitis, acute . . . . .	8	..	8
Cellulitis, acute . . . . .	9	..	9

Abscesses considered to be associated with filariasis developed in 2 soldiers, following cellulitis of the elbow region. On incision, these abscesses were deep and had many pockets which had to be broken up in order to effect complete drainage. The pus obtained was thin, greenish in color, and showed no organisms on direct microscopic examination. These lesions closely resembled the abscesses described below, which were observed among natives.

A quite different type of swelling occurred in some of our patients. This was a soft, non-suppurative swelling with no sign of acute inflammation, affecting an area 3 to 6 inches in diameter on the arm, hand, or leg. In a few instances more than one of these swellings was found at the same time in the same individual. Some 6 patients developed

similar swellings of the upper eyelid. A number of men had urticaria at the time swellings of this type were present. All of these swellings were transient. As a result of our experience, we came to consider the multiple occurrence and transiency of these peculiar lesions as important diagnostic findings.

Fever was only observed in significant degree when acute cellulitis or lymphangitis was present.

**Blood Counts.** As has been previously stated, our laboratory facilities were simple and elaborate examinations were out of the question. Red blood cell counts showed no significant anemia. White blood cell counts showed a moderate increase when cellulitis or lymphangitis and fever were present, but were otherwise within normal limits. In early cases the differential white cell count was usually normal. After 2 or 3 weeks' illness, however, the eosinophils were often increased. Among 127 patients, 56 (44%) showed more than 4% eosinophils, the maximum count being 44% (Table 2). Thick blood smears were studied with great care in 100 of our Army patients and failed to show any suggestion of a microfilaria.

Material to use in the performance of skin tests was not available.

TABLE 2.—PERCENTAGE OF EOSINOPHIL CELLS FOUND IN 127 PATIENTS

Eosinophils (%)	No. of patients
1 to 2 . . . . .	35
4 . . . . .	36
6 to 9 . . . . .	39
10 to 19 . . . . .	12
20 to 29 . . . . .	4
44 . . . . .	1

**The Course of the Disease.** Since the clinical findings and course comprise one of the most important approaches to the problem under discussion, it seems desirable to recapitulate these aspects of the disease. Patients first presented themselves from 3 to 14 months after first arrival in this area. The earliest symptoms, malaise, insomnia, anorexia, nausea, vomiting, and pain in various parts of the body, were not suggestive of any specific diagnosis. After an interval of about 2 weeks, pain, tenderness, and swelling appeared in the scrotal contents and spermatic cord as described above. Some of the patients developed the signs of acute lymphadenitis and lymphangitis, usually of the upper arm and thigh. Severe pain, marked swelling and acute lymphangitis required hospitalization, but usually subsided in a week or two. However, symptoms and signs usually persisted in some degree for several weeks, during which the patients were ambulatory. During this period, there was much variation from day to day in the severity of the disease. Both symptoms and swellings were aggravated by exertion and on hot, humid days; rest and cool weather had the opposite effect. In most cases an interval of freedom from trouble followed. Recurrences appeared, however, in the patients that remained under observation, after 1 to 3 months. As seen on the island, recurrent attacks appeared to be increasingly severe and persistent. Observations were cut short by the evacuation of patients.

**Epidemiologic Considerations.** It was observed that the incidence of the disease in the various units of troops on the island bore a relation to the proximity of camps and other military installations to native villages and to the frequency of mingling of soldiers and natives at work. Our installation was situated within 50 yards of a native village, and a native house, in which lived proved carriers of filariasis, was situated within the hospital grounds. Natives going to and from the village frequently traversed the grounds. The members of the hospital unit developed an incidence of 50% in a year. Many attended the dispensary and some were regularly employed on the hospital grounds.

The men of a certain service unit were found after 12 months to be affected to the extent of 28%. This unit was located several hundred yards from native villages, but many natives were regularly employed in the work of the unit in close proximity to its own members.

In contrast with this experience, the incidence of the disease among the personnel of a group of units stationed some 5 miles from any native village was only 6% at the end of a year. The men of these units had little daytime contact with natives.

These differences in incidence are of special interest in the light of the fact that all soldiers on the island had frequent contacts after sunset with natives in the moving picture theatre, at dances, and in the villages. If the disease had been transmitted at night, one would have expected an approximately even distribution in the various military units.

Examinations of natives of the island, which are further described below, showed that many of them had typical fully developed elephantiasis. Blood smears made in a series of 100 individuals showed numerous microfilariae in 40%. There was no discernible periodicity in this parasitemia, as microfilariae were found at all hours of the day, as well as at night.

The commonest mosquito on the island was identified by area entomologists, from both larval and adult forms as *Aedes scutellaris*. It was estimated that this species accounted for 95% of the large mosquito population of the island. Our experience showed that the species was clearly a day-biter. A small number of culicine mosquitoes were found which were not further identified. No example of *Culex quinquefasciatus* or *Anopheles* was discovered.

Mosquito breeding places abounded everywhere on the island, which was pockmarked with small crevices in the coral surface. Innumerable broken coconut shells helped to hold the water in these depressions. It was an impossible task to clear large areas and only very gradually were the grounds immediately about army sites cleaned up.

**Diagnosis.** When the patients we have described were first seen, no diagnosis could be made. As the clinical picture became clearer with the occurrence of well-marked lesions and the number of patients increased, the presence of microfilariae in the blood of a high percentage of natives, together with a high density of a known vector, led to a tentative diagnosis of filariasis. This diagnosis was not proved, since neither microfilariae nor adult worms were ever demonstrated in any



of our patients. We were informed that medical officers on other Pacific Islands known to be filarial had an experience similar to ours, and that, in a number of patients closely corresponding to those reported here, adult filariæ were found in sections of excised lymph nodes. We have not heard of the demonstration of microfilariae in any Army patients of this group.

The status of skin tests, precipitin tests, and complement-fixation tests, which were not available to us, in the diagnosis of filariasis appears to be uncertain at present.

An epidemiologic basis for the diagnosis has been presented above. Close proximity over a prolonged period of time to natives carrying microfilariae in their blood without adequate protection against the mosquito vector is to be emphasized. The relation we have described between variations in incidence and contact with natives is important.

The nature and course of the symptoms and lesions described appears to be well explained by the diagnosis of filariasis. In connection with epididymitis, the possibility of gonorrhea was studied, but the differentiation on the basis of history, lack of response to treatment, and associated funiculitis is not difficult. Funiculitis is well recognized in filariasis, but rare in other diseases. Varicoceles were found difficult to evaluate and were given no great weight. Hydroceles, which were not found among our patients, are said to be common in filariasis. The lymphangitis described above, especially in regard to its spread to instead of from, the periphery, and its persistence, is apparently highly characteristic of early filariasis. Among the troops on the island, there were many cases of streptococcal lymphangitis which was readily distinguishable by its acute severity, its centripetal spread, and its response to treatment.

A difficult diagnosis was presented by the case of a patient with pain, tenderness, and stiffness in the right lower quadrant of the abdomen. Nausea, vomiting, slight fever, and slight leukocytosis were present. Operation was performed, but the appendix was considered normal; enlarged mesenteric lymph nodes were present. It is possible that this patient had filariasis, as many other patients in the group we have described had similar symptoms and signs which, however, were less characteristic of appendicitis.

As to the course of the symptoms and lesions, the outstanding features were the persistence for a relatively long period, with marked day-to-day variations in severity, the lack of response to any form of treatment, except perhaps rest; and the frequent recurrence after an interval of freedom.

**Treatment and Disposition.** There is no known specific treatment for filariasis. Hence, we had to rely upon symptomatic therapy. In the acute phases, bed-rest and occasional sedatives were found to be the most effective measures. Severe pain and swelling of the spermatic cord and scrotal contents were treated to some effect by elevation and the application of an ice-cap. Acute lymphangitis was treated by elevation of the arm or leg and the application of hot, moist compresses. In most cases of lymphangitis, sulfadiazine was given without

appreciable benefit. In the intervals between acute attacks, limitation of physical exertion was both necessary and beneficial.

Reassurance of the patients, many of whom were greatly disturbed by fear of developing elephantiasis which they saw daily in natives, was found to be both important and effective. We did not encounter among our patients any severe or resistant instances of untoward mental reaction based on the involvement of the genitalia. In this connection, the soldiers were aware that natives with elephantiasis had many children.

In accordance with the policy of the Army, patients with the diagnosis of filariasis were evacuated, with no great delay and usually directly, to the United States. In some instances this was done by air, but more often by sea. Patients who had had the more severe lesions were given preference in time of evacuation over others. (Army policy further requires the restriction of individuals with the diagnosis of filariasis to duty within the limits of the United States.) It should be noted that unless these individuals develop microfilariae in the circulating blood, they cannot be regarded as a source of infection for others.

**Prognostic Indications.** The prognosis of the cases we have described cannot be stated with certainty. Nevertheless, there are many indications which suggest that the likelihood of their developing severe late lesions, including elephantiasis, is small. Natives are infected repeatedly throughout their lives, beginning in young childhood. Elephantiasis, even in heavily infected populations, is rarely seen at a younger age than the twenties. Many natives, though their blood teems with microfilariae, apparently never develop severe lesions of any sort. It is believed that the early removal of infected soldiers from endemic areas and the careful avoidance of reinfection may protect our soldiers, at least in most instances, from the late manifestations. In view of the bad psychologic effects of uncertainty and fear, it is clearly best for the individuals concerned to take as hopeful a view of the future as possible.

**Suggestions for Control.** On the basis of our experience, a brief discussion is given of the control of filariasis under similar circumstances. Mosquito control is the only satisfactory approach to the problem.

If adequate mosquito control is impossible and close contact with natives is inevitable, prolonged exposure in endemic areas should be avoided.

**Filariasis Among Natives.** A comparison of the clinical picture we have described among American soldiers with filariasis in native inhabitants of the island is of interest. The number of people on the island is unknown, since it is many years since a census was undertaken. The incidence of filariasis is also not known with accuracy. As was stated above, 40% of over 100 natives who were examined were found to have microfilariae in their blood. We have also reported that this parasitemia was present at all hours of the day and night. Presumably the total incidence in natives is higher than is indicated by our results, since early infections are not associated with parasitemia. Moreover,

blood smears in many cases of elephantiasis among natives failed to show microfilariæ.

Some of the manifestations attributed to filariasis were seen in natives of all ages. The children of the island go naked up to the age of 8 or 10 years, so that infection must occur frequently at an early age. Microfilariæ are not found in the blood, however, before the age of 3 to 5 years. One 6 months old baby was treated surgically by us for multiple abscesses of the type described below, which is considered throughout this endemic area to be due to filariasis. Elephantiasis was seen among aged natives.

From a clinical point of view, it is remarkable that very few inhabitants of the island, even among those with elephantiasis, were incapacitated by filariasis. The large majority of natives was quite capable of regular work. As is well known, the presence of microfilariæ in the blood in itself is asymptomatic. The acute manifestations, which we have described as occurring in American soldiers, were seen in natives in only a few instances. It is possible that those who grow up on the island rapidly acquire a partial tolerance to the infection, which accounts for the absence of such manifestations.

Acute exacerbations of a type different from the picture seen in early cases, however, were frequently seen in natives. The commonly recognized picture is called filarial fever. The islanders are thoroughly familiar with these attacks, all of which they consider to be of the same nature. The symptoms closely resemble those of brief, severe influenza. The temperature sometimes rose to 103° F. Severe generalized aching, chills, and prostration were common. In 3 or 4 days the attack was over. Convalescence was notably rapid.

The peculiar abscesses which have been described as occurring in a few American soldiers, were common among natives, several hundred of them having been treated by us. In a single instance a filaria was found in an abscess. The commonest site was the internal part of the upper third of the thigh. Another favored location was under the rectus fascia in the right lower quadrant of the abdomen, where an appendiceal abscess was suspected but disproved. Unusual sites were the retroperitoneal tissue of the lumbar region and the popliteal space. This type of abscess was frequently multiple. A native who died following epileptiform seizures, was found on postmortem examination to have abscesses in the brain, under the left rectus, and in both feet.

Such abscesses developed slowly and were resorbed equally slowly. Patients became markedly prostrated and appeared "toxic." The temperature rose as high as 104° F. Pain about the abscess was severe. On examination, these abscesses were deep. For some time, they felt indurated and suggested neoplastic rather than inflammatory masses. In some cases a connection with bone was suggested at first, leading to the impression of an osteogenic sarcoma. In the course of time, abscesses were observed to soften as suppuration occurred. Because they were usually beneath deep fascial planes, they rarely pointed to the skin. In a few cases they were seen to resorb spontaneously. In general, incision and drainage were considered essential

after softening had taken place. Usually many communicating pockets were found, indicating a marked tendency to burrowing. The pus which was removed was odorless, thin, and greenish. Smears showed numerous pus cells, but bacteria were rarely present.

The principal chronic manifestations of filariasis in natives, apart from parasitemia, were lymphadenopathy and elephantiasis. The inguinal region was the most frequent site of lymphadenopathy. On physical examination, involved lymph nodes were difficult to distinguish from massive tuberculous nodes. Figure 1 shows a young adult native with severe bilateral inguinal lymphadenopathy. This case is characteristic of late involvement of filariasis.



FIG. 1.—Native with severe inguinal lymphadenopathy due to filariasis.

The pathogenesis of elephantiasis is the subject of controversy, which will not be discussed here. Allowing for the fact that early elephantiasis is often hidden by natives, a conservative estimate of the incidence is 5%. Cases were not uncommon in islanders in their twenties and thirties. As a general rule, since they have grown up with the disease, the natives can give few historical data on its development. Occasionally a story of numerous attacks of what was taken to be acute lymphangitis was obtained. One native with severe and extensive elephantiasis alleged that he had first noticed the development of the process 2 years before. More often, the first signs of the advanced lesions we saw had been observed 5 or 6 or more years earlier. Americans on the island were all impressed by the fact that

few natives were incapacitated by extensive elephantiasis. Islanders with massive enlargement of the legs frequently participated in dances.

Among the natives of both sexes, the commonest site of elephant-

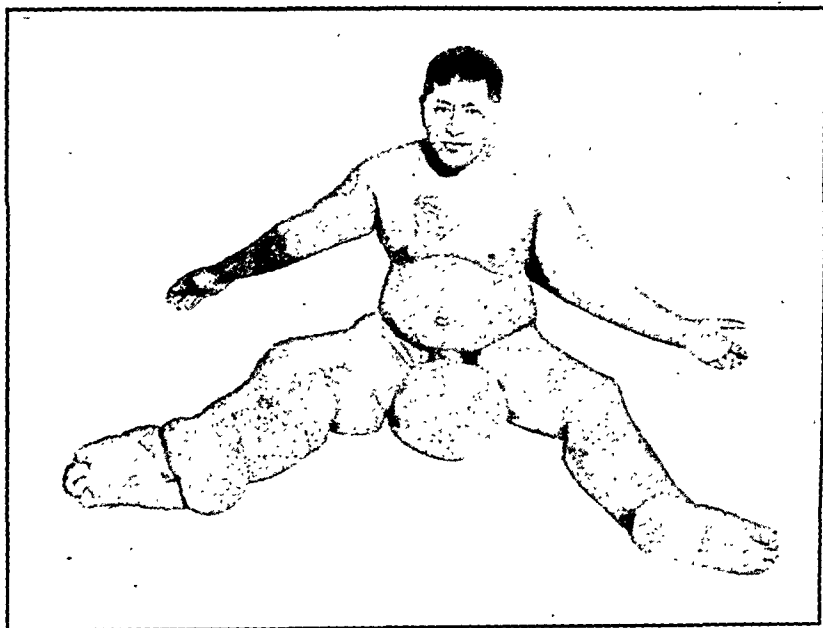


FIG. 2.—Native, aged 44, with severe elephantiasis of scrotum and legs.



FIG. 3.—Native with elephantiasis of arms and scrotum and chronic inguinal lymphadenopathy.

iasis was the thigh and leg. In males, the scrotum was frequently involved, either alone or in association with the legs. Figure 2 shows a male islander of 44 years, who had the most extensive elephantiasis we saw. Lesions were alleged to have been present for only 6 years. The man was unable to walk and sat continuously in his hut, occupied in making grass mats and skirts. An operation had been attempted some 2 years before we saw the individual, but no benefit was apparent. Marked elephantiasis of the arm was rarely seen. Figure 3 shows a native with massive involvement of both arms; the scrotum and inguinal nodes are also shown to be enlarged. Elephantiasis of the breast was often seen in females, although it is rarely described. Figure 4 shows a marked case in a woman who also has elephantiasis of the right leg.



FIG. 4.—Female native with advanced elephantiasis of both breasts.

A case of some interest was that of a European trader who, after 4 years of living on islands where filariasis is endemic, developed attacks of filarial fever. These attacks recurred, according to the history, about every 3 months for over 3 years. At the end of that period, swelling of the scrotum and both legs began to appear. The febrile attacks ceased soon after elephantiasis began to develop. A futile operation had been performed on this man's scrotum before we saw him.

**Summary.** An account is given of the development among American soldiers on a filariasis-endemic Pacific Island of clinical signs and symptoms, which are attributed to early filariasis. *Microfilariae* were

not found. The clinical picture was characterized by recurrent attacks of illness with transient lymphadenitis, lymphangitis, and swelling of the arms or thighs. Lymphangitis always spreads peripherally. There was no indication of the development of elephantiasis. Certain epidemiologic aspects of the incidence of the infection among troops are discussed. The vector is regarded as *Aedes scutellaris*. Suggestions are given for the control of filariasis. The belief is expressed that early evacuation from the endemic region and avoidance of future exposure to further infection with the disease should minimize the danger of the development of permanent late lesions in these soldiers. Filariasis among natives of the island is briefly described. Of those examined by blood smear 40% had microfilariae in their blood. At least 5% had elephantiasis.

## 7. SUMMARY OF A 3-YEAR STUDY OF THE CLINICAL APPLICATIONS OF THE DISINFECTION OF AIR BY GLYCOL VAPORS\*

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THE clinical application of air disinfection by glycol vapors has been investigated for a period covering 3 winters at the Children's Seashore House in Atlantic City. A large part of this work has been reported previously in considerable detail.<sup>1,2</sup> These studies involved primarily the determination of the rate of incidence of respiratory infections in groups of patients whose air supply was largely disinfected, and in control groups.

This institution, a convalescent home, was selected because the prevailing conditions were peculiarly well adapted to the exhibition of the clinical effects of air disinfection. The patients were divided by age and sex into groups of 16, each of which occupied a ward. These wards were distributed on 2 floors of a building, the wards on the upper floor having the same size, position, exposure and window space, respectively, as those below them. The distribution of diagnoses did not vary markedly among the wards, so that the structure of the House provided pairs of wards, each well suited for control observations with respect to the other.

The patients were largely rheumatic or orthopedic, most of them bedfast, so that physical contact among patients was relatively small in extent. They were, however, not acutely ill, so that physical contact with nursing and attendant staff was not close. Accordingly, direct cross-infection or direct droplet hits were relatively less impor-

\* These investigations were aided in part through the Commission on Air-borne Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army; Preventive Medicine Division, Office of The Surgeon-General, U. S. Army.

tant in the transmission of respiratory pathogens, and droplet nuclei and infected dust more so. Some pairs of beds were contiguous, except during a respiratory episode affecting the occupant of such a bed, and toys and books were transferred at times, although infrequently, from bed to bed.

There was no contact among patients from different wards, since each of the classes held in the schoolroom for the small number of ambulatory patients was limited to patients from a single ward.

During the warmer part of every fair day, except very cold ones, all beds were wheeled to open porches adjoining the respective wards. For the remaining part of the 24 hours the beds were in the wards, and during that part of the day a minimum of outside air was admitted to the wards, in order to conserve heat. The operation of the vaporizing units was continuous.

**Methods.** Propylene glycol was used as the disinfecting agent during the preliminary observations of the winter of 1941-42 and the following year. In the past winter, 1943-1944, tri-ethylene glycol was used.

The method of vaporization was the same for both agents. The glycol was kept at a constant level in an insulated beaker, which was supplied from a reservoir. In the beaker was immersed an electrical resistance coil of whatever wattage-rating and resistance were necessary to vaporize the required amount of glycol per hour, when used directly on the house line of 110 volts. A small electric fan was placed before the vaporizer in order to pull the glycol vapor stream and disperse it into the air nearby.

The degree of disinfection of air was determined by settling plate counts, the results being expressed in colonies per Petri plate. Comparisons were made in experimental and control wards, the exposure period being 30 or 60 minutes, depending on the time of day.

Determinations of the concentration of glycol vapor in air were made according to the method of Puck<sup>3</sup> for propylene glycol, and the method of Wise, Puck and Stral<sup>4</sup> for tri-ethylene glycol.

The maintenance of adequate relative humidity was not found to constitute a problem, since readings in the wards at semi-weekly intervals ranged between 30 and 40%, usually above 35%.

**Plan of Experiments.** In planning the experiments, the wards of the Seashore House were divided into pairs, each pair consisting of wards similarly placed on the second and third floors. Glycol was vaporized alternately, first in one ward of the pair and then in the other during successive 3-week periods, the opposite member serving as a control. Three-day intervals were allowed between periods of observations for infections in a state of incubation. All observations, therefore, involve comparisons of two similarly placed wards at the same time, the wards differing only in that one contained glycol vapor in its atmosphere. A respiratory infection was defined as a clinically recognizable episode with some objective manifestation in addition to fever. Thus a sore throat was included only if it showed an inflamed nasopharynx on examination; a "common cold," or painful ear was included only if a discharge or evidence of inflammation was present, and a cough was included only if productive.

Observations were made of the rate of incidence of respiratory infections, bacterial settling plate counts, and concentration in air of the glycol vapor.

**Results.** *The Incidence of Respiratory Infections.* The rate of incidence of respiratory infections was markedly lower in wards containing the glycol vapor (Table 1).

The upper respiratory infections observed included coryza, tracheobronchitis, nasopharyngitis and otitis media. In the first and third



winters, there was no marked preponderance of any of these particular diseases. During the winter of 1942-43, however, coryza accounted for a majority of all observed infections. In view of the fact that the common cold is probably caused by a filterable virus or filterable viruses, while the other diseases observed are caused by bacteria, a finer analysis of the data for that year is given in Table 2.

TABLE 1.—THE RATE OF INCIDENCE OF RESPIRATORY INFECTIONS IN EXPERIMENTAL AND CONTROL WARDS

Winter	Glycol used	Ward-weeks	Respiratory infections	
			Experi- mental	Control
1941-42	Propylene	8	2	16
1942-43	Propylene	54	5	100
1943-44	Tri-ethylene	19	6	16*
		81	13	132

\* The actual number of 26 infections in 31 ward-weeks has been reduced in proportion to 19 weeks for comparison with the 19 ward-weeks of observations in glycol-vaporized wards.

TABLE 2.—THE DISTRIBUTION OF RESPIRATORY INFECTIONS BY DIAGNOSIS (1942-43)

Disease	Number	
	Glycol	Control
Common cold . . . . .	3	79
Tracheobronchitis	2	21
Otitis media		
Pharyngitis, acute		

*The Bacterial Population in the Air.* The relative reduction in the population of viable bacteria in the air as indicated by settling plates was greater and more constant in the course of vaporization of propylene glycol than tri-ethylene under the conditions of these experiments, probably because of the narrower range between bactericidal and condensing concentrations in the case of the latter. Because of this narrow range, it was difficult to maintain a minimum concentration of tri-ethylene glycol vapor in air as much above the effective bactericidal concentration as in the case of propylene glycol with the vaporizing devices used in this study. Average values of all determinations are shown in Table 3.

TABLE 3.—THE BACTERIAL SETTLING PLATE COUNTS IN EXPERIMENTAL AND CONTROL WARDS

Year	Glycol	Mean plate counts		
		Glycol	Control	Ratio control/ glycol
1942-43	Propylene*	13.4	81.3	6.05
1943-44	Tri-ethylene	18.3	75.3	4.12
	Number of counts:	114	46	
	Standard error of mean:	0.9	2.2	

\* Individual counts given in original report.<sup>2</sup>

*The Concentration of Glycol Vapor.* The concentration of propylene glycol vapor in air was maintained in the neighborhood of one part in 15,000,000 (0.069 mg./liter). Concentrations at various times and in

different parts of the experimental wards ranged from 0.048 mg./liter to 0.094 mg./liter.

In the case of tri-ethylene glycol the maintenance of a satisfactory concentration presented a greater problem, because of the narrow range between bactericidal concentration and precipitating concentration mentioned above. In the absence of sensitive methods for regulating or measuring concentrations of tri-ethylene glycol vapor in air, a rate of vaporization sufficient to disinfect the air to a considerable degree was often found to produce precipitation of glycol on windows, floors and objects in the ward. The concentration of this vapor in air ranged between 0.0018 mg./liter to 0.0033 mg./liter.

The vaporization of propylene and tri-ethylene glycol in bactericidal concentrations has in these experiments been shown to cause a reduction in the total incidence of respiratory infections.

**Discussion.** The difficulties encountered in this study in the use of tri-ethylene glycol are due largely to the early stage of engineering development of the field and to the relatively small size of the enclosed spaces involved. In a larger volume of air, the fluctuations in glycol concentration caused by occasional opening of doors, etc., would be proportionately smaller and the concentration could be maintained in a narrower range. Because of the greater range of bactericidal concentrations of propylene glycol, it was technically the preferred glycol under the conditions of our experiments. The ultimate development of devices to regulate the rate of vaporization of tri-ethylene glycol by the concentration of the vapor present in air at the moment may obviate the difficulties we found in using this disinfectant and permit workers to take advantage of its higher disinfecting potency.

At the present writing, however, it would appear that for small spaces and in the absence of refined devices to regulate the rate of vaporization of glycol, propylene glycol is the agent of choice in small wards, offices and spaces of similar size.

In considering the application of these results to other situations, it is well to allow for the peculiarly favorable circumstances at the institution chosen for the experiments.

First, the generally inactive character of the institution and the absence of acutely ill children resulted in a considerably smaller extent of traffic into and out of the ward. Again, the patients were within the enclosed space of the ward only during the colder part of the day and at night. These factors not only reduced the total air exchange rate, but decreased the degree of fluctuations of concentration of glycol vapor in air.

The character of the patients also provided exceptionally favorable experimental conditions. Most of the children were bedfast, since the great majority were convalescing rheumatic and orthopedic patients. Of the latter, the majority were fixed in a supine position by casts, breast straps or extension weights. As a result, there was relatively much less direct contact or direct droplet hits than would be expected in a group of children, and correspondingly even a greater quantitative importance of droplet-nuclei in cross-infection. Again, in most of the

bedfast and all of the supine children, expulsion of infectious material and viable bacteria was largely in an upward direction, and the time of exposure to the glycol vapor was probably considerably longer, in general, than in other situations.

Finally, it is important that during the experimental periods in any ward, glycol vapor was present in the air supply of the subjects during all of the time spent indoors.

These favorable circumstances are, however, largely of quantitative significance. Under other conditions, a higher concentration of glycol in the air or controls on sudden shifts of masses of air into the ward or room might be necessary. The studies described here have demonstrated that the disinfection of air by glycol vapors can be successfully applied to the problem of prevention of air-borne cross-infection.

**Summary.** The disinfection of air by the vapor of propylene glycol and tri-ethylene glycol has been applied to the clinical problem of the transmission of air-borne cross-infection in a home for convalescent patients. A marked decrease was observed in the total rate of incidence of upper respiratory infections among those patients whose air-supply was largely disinfected by glycol vapor.

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## 8. EXPERIMENTAL AIR-BORNE TUBERCULOSIS\*

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*Air-borne Contagion of Tuberculosis in an Animal Room.* If normal guinea pigs<sup>1</sup> are placed in individual cages in a room housing tuberculous animals, the exposed pigs acquire tuberculosis of respiratory origin as evidenced by pulmonary lesions, massive tuberculous involvement of the tracheobronchial nodes draining the pulmonary portal of entry and the absence of any disease in the mesenteric or cervical nodes draining the alimentary portal. As is well known, tuberculosis characteristically leaves the traces of its progression in the body by the involvement of the nodes draining the portal of entry.

As may be seen in Figure 1, guinea pigs situated at a considerable distance from their tuberculous room-mates acquire tuberculosis just as often as the guinea pigs placed in immediate proximity to tuberculous animals. Therefore, we may assume that the contagion is uniformly distributed in the room and, since the disease is respiratory in origin, the contagion is air-borne.

*Method of Studying Air-borne Contagion of Tuberculosis in Inbred Rabbits of Varying Resistance to the Disease.* A large manifold<sup>2</sup> is

\* Aided by a grant from the Commonwealth Fund.

separated in the middle by a fine wire mesh screen (Fig. 2). On one side of the screen there is a run for artificially infected rabbits which shed tubercle bacilli in their urine. On the other side of the screen,

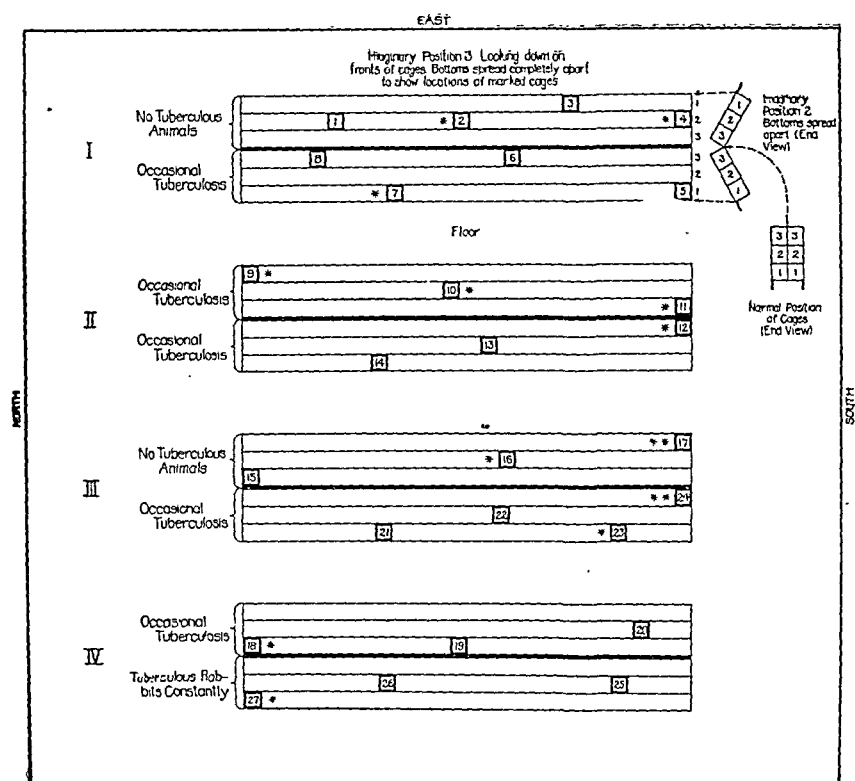


FIG. 1.—Plan of location of cages of tuberculous and non-tuberculous animals. Each asterisk indicates a guinea pig which acquired tuberculosis.

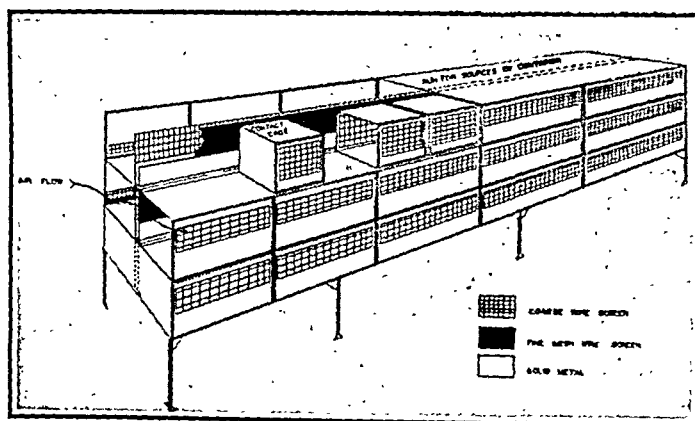


FIG. 2.—Special cages for the study of air-borne tuberculosis in rabbits.

in individual cages with open wire meshwork in back and in front, are placed members of highly inbred rabbit families. By means of tuberculin tests and Roentgen rays the onset of tuberculosis is determined. The disease thus acquired is of respiratory origin and begins as a single

primary focus in the lung, which is always associated, in animals of low genetic resistance (Fig. 3) with a massive tuberculous involvement of the draining tracheobronchial nodes and extensive hematogenous generalization. In the resistant animals (Fig. 4) the disease tends to remain localized to the portal of entry without involvement of the draining nodes and little hematogenous generalization. The disease acquired by these families closely corresponds to the different types of tuberculosis seen in man.



FIG. 3.—Organs of susceptible rabbit F4-33. Duration of disease, 3.3 months. Large, completely caseous primary focus in middle of left lung without softening. Extensive enlargement and massive caseation of homolateral draining tracheobronchial nodes. Corresponding structures on right side not involved. Large nodular caseous tubercles of hematogenous origin in both lungs. Primary, rapidly progressive, generalized tuberculosis with extensive disease in the kidneys, pleura and knee joint.

*The Prevention of Natural Air-borne Contagion of Tuberculosis in Rabbits by Ultraviolet Radiation.* The room housing the manifold is divided by a solid partition<sup>3</sup> extending from the floor to the ceiling, which also divides the interior of the manifold into 2 equal air-tight halves (Fig. 5). One room is not irradiated. The other room is irradiated. Ultraviolet lamps are placed horizontally in the space between the infected and exposed animals in each of the 3 tiers. In addition, the air of the experimental room as a whole is irradiated by ultraviolet lamps placed above and below this section of the manifold. Litter-mates of highly inbred families of high and low resistance are placed in corresponding positions in the contact cages of both rooms. The infected rabbits serving as sources of contagion are interchanged daily between the two rooms. Thus both the host and parasite variables are equalized.



FIG. 4.—Organs of resistant rabbit A2-6. Duration of disease, 9 months. Single, large, well-encapsulated cavity in the right lung. Draining tracheobronchial nodes normal. Tuberculosis analogous to the "reinfection type," with tubular spread to the entodermal tract, including larynx and intestines, with ulceration in the colon. Mesenteric nodes normal. Kidneys normal. Non-progressive, uniformly distributed, nodular tubercles in both lungs of hematogenous origin.

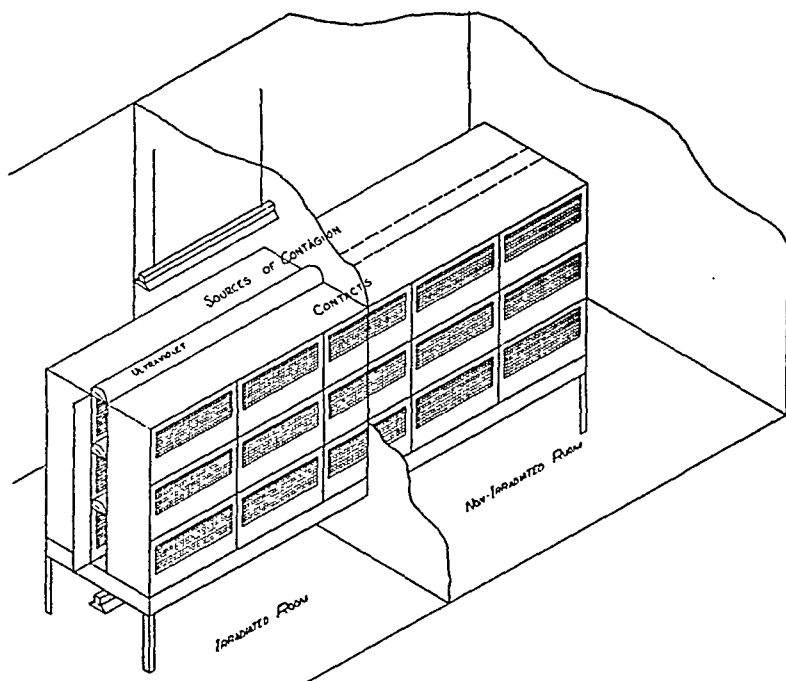


FIG. 5.—Set-up of cages of irradiated and non-irradiated animals.

At the end of a year (Table 1) 11 of the 15 contacts in the unirradiated room died of tuberculosis. These included rabbits of high and low resistance to the disease. None of the 15 litter-mates exposed to the same contagion in the irradiated room developed tuberculosis. Three additional rabbits in the control room developed tuberculin sensitivity without any tuberculous changes at autopsy. None of the protected rabbits developed tuberculin sensitivity. Only one rabbit in the irradiated room developed a regressive microscopic tubercle. Thus a 73% mortality from tuberculosis was eliminated by ultraviolet radiation. That the intensity of contagion involved in this experiment is much greater than occurs in human life can be appreciated from the fact that only 1% of human beings exposed to household contagion acquire tuberculosis in 1 year. It is probable, therefore, that ultraviolet radiation may control air-borne contagion of human tuberculosis.

TABLE 1.—THE EFFECT OF ULTRAVIOLET IRRADIATION ON NATURAL AIR-BORNE CONTAGION OF TUBERCULOSIS IN CONTACTS OF RABBIT FAMILY A, OF HIGH INHERITED NATURAL RESISTANCE, AND IN FAMILIES C AND F, OF LOW INHERITED NATURAL RESISTANCE TO THE DISEASE (EXPERIMENT OF 1942-43)

Family	Rabbit No.	Duration of exposure (mos.)	No. of times tuberculin positive	Maximum tuberculin reaction in mm. <sup>2</sup> of inflammation	Killed (K) or died (D)	Extent of tuberculosis at death
<i>Rabbits Exposed in Unirradiated Room</i>						
A	A8=19	5.6	7	368	D	++++
	A8=51	6.3	7	741	D	+++
	A7=26	7.3	7	372	D	++++
	A8=43	9.7	4	475	D	0
	A7=31	10.8	15	1350	D	0
	A8=29	11.6	7	150	K	++
	A7=36	11.6	11	260	K	++
	A7=44	11.6	0	...	K	0
C	C6-9	5.2	7	1330	D	++++
	C6-32	5.7	7	432	D	++++
	C5-50	6.1	7	672	D	++++
	C6-26	9.2	2	213	D	++
	C6-1	11.6	3	153	K	0
F	F6-25	8.8	4	342	D	++++
	F6-14	10.4	3	141	D	++++
<i>Rabbits Exposed in Irradiated Room</i>						
A	A8=23	6.5	0	—	D	0
	A8=39	8.9	0	—	D	0
	A7=37	11.6	0	—	K	0
	A7=40	11.6	0	—	K	??*
	A8=49	11.7	0	—	K	0
	A7=28	11.7	0	—	K	0
	A8=52	11.8	0	—	K	0
C	C6-30	5.7	0	—	D	0
	C5-44	11.6	0	—	K	0
	C6-2	11.7	0	—	K	0
	C6-13	11.7	0	—	K	0
	C6-31	11.7	0	—	K	0
F	F5-27	11.7	0	—	K	0
	F6-21	11.8	0	—	K	0
	F6-15	11.8	0	—	K	0

\* Guinea pig inoculation of a questionable pulmonary lesion demonstrated living, virulent tubercle bacilli.

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*Resistance to Attack by Air-borne Tubercle Bacilli and Resistance to the Progress of the Ensuing Disease.* One inbred family has little resistance to attack by tuberculosis<sup>4</sup> as indicated by the short interval between the beginning of exposure and the acquisition of a positive tuberculin reaction. Yet it succumbs to a slowly progressive, localizing disease which is of considerable duration, indicating considerable resistance to the progression of the naturally acquired disease. See Table 2.

TABLE 2.—THE RELATION BETWEEN THE RAPIDITY OF ATTACK BY NATURAL AIR-BORNE CONTAGION OF TUBERCULOSIS AND THE DURATION OF THE ACQUIRED DISEASE IN FAMILY A, OF HIGH RESISTANCE, AND FAMILIES F AND C, OF LOW RESISTANCE TO THE INFECTION

A family			F family			C family		
Rabbit No.	Pre-allergic period (mos.)	Duration of disease (mos.)	Rabbit No.	Pre-allergic period (mos.)	Duration of disease (mos.)	Rabbit No.	Pre-allergic period (mos.)	Duration of disease (mos.)
A8=19	0.9	4.7	F4-25	1.9	3.8	C6-9	1.3	3.9
A8=29	1.3	10.4	F4-30	2.4	3.0	C2-8	2.0	9.5
A7=31	1.8	—	F2-15	3.0	6.2	C6-32	2.1	3.6
A8=43	1.8	—	F5-2	4.6	—	C5-50	2.3	3.9
A4-4	2.0	—	F6-25	5.1	3.7	C4R-2	2.7	4.3
A8=51	2.3	4.1	F2-3	6.0	5.0	C5-30	3.0	3.3
A7=26	2.3	5.0	F5-14	6.0	—	C4S-9	3.3	tbc. + snuffles
A3=3	3.2	11.5	F4-33	6.2	3.0	C2-6	3.7	3.7
A6=21	3.3	—	F3-9	6.5	8.0	C4S-11	3.8	tbc. + snuffles
A5=3	3.3	12.9	F6-14	8.3	2.1	C4R-6	4.7	3.8
A5=4	3.3	—	F3-7	11.0	3.5	C4S-30	4.9	—
A5=21	3.3	10.7	F4-11	11.7	4.0	C2-1	5.0	3.0
A7=5	3.5	—				C6-1	5.5	—
A7=36	3.6	8.0				C2-7	7.0	5.0
A5=2	4.3	—				C6-26	8.3	tbc. + snuffles
A7=10	4.9	—				C5-14	9.0	2.6
A2=11	5.0	7.5				C2-18	11.9	—
A7=4	6.0	—						
Average: 3.1±1.3 8.3±3.1			6.1±3.0 4.2±1.7			4.7±2.8 4.2±1.8		

P of pre-allergic period between A and F = 0.999.

P of duration of disease between A and F = 0.999.

P of pre-allergic period between A and C = 0.976.

P of duration of disease between A and C = 0.999.

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Another inbred family has considerable resistance against attack by natural air-borne contagion of tuberculosis as indicated by the long interval elapsing between the beginning of exposure and the onset of a positive tuberculin reaction, but the acquired disease is rapidly progressive, disseminating in type and of short duration, indicating little resistance to the progression of the naturally acquired disease. Resistance to attack by air-borne contagion of tuberculosis is therefore distinct from the resistance to the progression of the ensuing disease. "Anfälligkeit" is distinct from "Hinfälligkeit."

*The Effect of Increasing Concentrations of Air-borne Tubercle Bacilli on Rabbits of High and Low Genetic Resistance to the Disease.* If rabbits of high and low genetic resistance to the disease are simultaneously exposed in different experiments to increasing concentrations of air-borne tubercle bacilli,<sup>4</sup> the effect of this increment is different on animals of high and low resistance. The concentration of air-borne tubercle bacilli is varied by the route of infection used to inoculate the



rabbits serving as sources of contagion. Intravenous inoculation yields fewer rabbits which shed tubercle bacilli in their urine than when the rabbits are inoculated directly in the kidney. The concentration of the infectious agent can also be reduced by using peanut shells instead of peat moss as bedding for the sources of contagion. The former do not adsorb the tubercle bacilli-laden urine as well as the latter, and hence reduce the number of tubercle bacilli-laden particles thrown up in the air by the sources of contagion. The concentration of tubercle bacilli in the air can also be reduced by introducing ultraviolet lights in the room. It was found that increasing concentrations of tubercle bacilli in the environment of the rabbits of high genetic resistance to the disease increase the incidence of the infection, accelerate the rapidity of attack, and affect the essential character of the disease in proportion to the concentration of the infectious agent.

In the rabbits of low genetic resistance to the disease, up to a certain level, increasing concentrations of the infectious agent also increase the incidence of the disease and accelerate its onset. The character of the disease, however, is not affected. It remains rapidly progressive and disseminating in type. Beyond this concentration further increment of the infectious agent has no effect on the incidence of the disease, the rapidity of attack or the character of the ensuing disease.

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### 9. THE PRESENT STATUS OF GLYCOL VAPORS IN AIR STERILIZATION

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THE practical effectiveness of glycol vapors in the control of infections acquired *via* the respiratory tract depends primarily upon how large a proportion of these infections is air-borne. In man, gradually accumulating evidence indicates that air-borne transmission of such infections as measles,<sup>31</sup> chickenpox,<sup>2</sup> streptococcal infection,<sup>1,6,7,9,18,32,33</sup> the "common cold,"<sup>8,12,27,30</sup> and other infections<sup>13,19</sup> is sufficiently important to encourage practical attempts at air sterilization. Such control may assume the form of a direct attack upon microorganisms

in the air, of an attack upon secondary reservoirs in floor dust and bed-clothing, or of a combination of these two methods. This review deals with progress which has been made in the employment of glycol vapors as an air sterilizing agent.

*Laboratory Investigations With Glycol Vapors.* In 1941, Robertson and his co-workers<sup>25, 26, 28</sup> announced that propylene glycol vapor was effective, in very small concentrations, against the following micro-organisms, when suspended in the air: Pneumococci, streptococci, alpha and beta, staphylococci, *H. influenzae*, *H. pertussis*, *Esch. coli*, *M. catarrhalis*, *B. subtilis*, and influenza A virus. An important advance was made when it was found that triethylene glycol acted in the same manner as propylene glycol, but in concentrations which were about one-fiftieth as great.<sup>29</sup> Many of these original observations have been confirmed by Henle and Zellat,<sup>14</sup> Henle, Sommer, and Stokes,<sup>15</sup> and Jennings and Bigg.<sup>16</sup>

*Field Tests.* To date, the results of three field tests are available. Harris and Stokes,<sup>12</sup> studying propylene glycol, and later triethylene glycol, in the ward of a children's convalescent home, encountered 100 miscellaneous respiratory infections in untreated wards, but only 5 in similar wards where propylene glycol was vaporized. Great reductions in total bacterial air counts, as measured by "settling plates," were recorded by these workers. Under the conditions of their tests, propylene glycol effected a reduction of 71%, and triethylene glycol a reduction of 97% in total air-borne bacteria. The Personnel of Navy Medical Research Unit No. 1<sup>21</sup> found reductions of 22 to 54% in total air-borne bacteria by propylene glycol (0.07 to 0.14 mg. per liter), but the number of tests performed was apparently very small.

In order to test the efficacy of triethylene glycol vapor upon a respiratory *pathogen* under natural conditions, the Commission on Air-borne Infections<sup>5</sup> conducted extensive tests upon hemolytic streptococci in army hospital wards. These investigations showed that triethylene glycol produced overall reductions of about 65% in air-borne hemolytic streptococci in scarlet fever wards and in measles wards where streptococcal cross-infections took place. However, when the vapor was employed in conjunction with oil treatment of bedclothing and floors, the reductions exceeded 90%. The combined treatment produced an atmosphere almost free of hemolytic streptococci, both during periods of ward activity and during "quiet" periods. The average concentration of triethylene glycol required to produce these results was 0.0045 mg. per liter of air.

*Factors Which Influence or Augment the Efficacy of Glycol Vapors.*

A. Relative Humidity: Glycol action is most effective in the middle ranges of relative humidity: 35 to 50%.<sup>22</sup> Though some effect is produced by the vapors when relative humidity is as low as 20%, more glycol is required. At higher humidities (75% or more), the air cannot hold enough glycol to be of any value.

B. Temperature: Low temperatures enhance the action of glycol vapors; high temperatures depress their effectiveness.<sup>22</sup> Bactericidal action is greater below 72° F. than above this point. This temperature

effect is proof that the bactericidal action of glycols is physical rather than chemical.

C. Dust and Lint Control: As indicated above, actual field tests have shown that triethylene glycol is more effective in combination with adequate lint and dust control than when used alone.<sup>5</sup> This is in keeping with the observation of Robertson<sup>24</sup> that moist micro-organisms are killed more rapidly by glycol vapor than dried organisms.

*Apparatus for Dispersing Glycol Vapors.* Four general types of vaporizing devices have been described:

A. Vaporization of the Liquid Glycol From a Hot Surface: This can be accomplished by any heat-producing unit, such as a radio resistor,<sup>22</sup> a soldering iron,<sup>11</sup> or an electric light bulb.<sup>20</sup> The vapor is then dispersed by suitably placed fans. When glycol is vaporized directly from heated surfaces, precautions should be taken to insure the temperature's remaining below the disintegration point of glycols, 260° F. Nothing is known of the toxicity of such disintegration products.

B. Passage of Air Over Revolving Evaporating Surfaces: Coey and Spiselman, of the Research Corporation,<sup>4</sup> have devised a vaporizer in which air is drawn past a battery of electric heaters, and then over a series of revolving evaporating disks which dip into a reservoir of liquid glycol. The glycol-laden air then escapes through a vent and is distributed by fans or through a duct system.

C. Boiling of Water-Glycol Mixtures: This method delivers both glycol vapor and water vapor into the air.<sup>17</sup> When heat is applied to an aqueous solution of glycol, water evaporates more rapidly than glycol, so that the glycol concentration of the solution rises. The increase in glycol concentration is associated with an elevation of the boiling point. When the temperature rises to a certain level, a thermostat opens a solenoid valve, which feeds water into the vaporizer. The water thus cools the solution to a point where the solenoid valve again closes. This instrument, described by Jennings and Bigg,<sup>17</sup> when set at 280° F., is calculated to deliver 0.04 lbs. glycol and 2.5 lbs. water per hr.

D. Atomization of Glycol-Water Solutions: Another glycol disperser described by Jennings, Bigg and Olson<sup>17</sup> utilizes, as its basic unit, a series of nozzles which spray the glycol directly into an air stream. The smaller droplets evaporate, while the larger ones are removed by a series of baffles. In practice, it is necessary to warm the air just before it passes the spray. The glycol-laden air is led into a duct system.

*Maintenance of Relative Humidity.* This is easily accomplished in steam-heated rooms by introducing steam directly into the room from the steam line. The hissing sound produced by the escaping steam can be eliminated by a suitable muffler. Also, the humidity can be regulated to within about 5% by inserting a solenoid valve between the steam line and the muffler, and controlling the operation of the valve by a human hair humidistat located in a convenient place in the room. Maintenance of adequate humidity in buildings where steam is not available, such as army barracks, is more difficult. So

far, no satisfactory answer to this problem has been found. Another method of raising the humidity is by boiling water-glycol solutions.<sup>17</sup>

*Regulation of Glycol Content of Air.* The ideal glycol concentration in the air is an amount just below saturation. If the level is lower than this, the bactericidal action is diminished. If it is higher, a visible fog will form. Though fogs are not harmful, they are psychologically undesirable. Puck, Wise and Robertson<sup>23</sup> have constructed a regulating device which automatically controls the concentration of glycol vapor in the air of a room, maintaining it just below the fog level.

*Toxicity and Inflammability.* Hanzlik and his co-workers have demonstrated a low degree of toxicity of oral or parenteral propylene glycol in experimental animals.<sup>10</sup> More important in reference to the use of glycol vapors for air sterilization has been the demonstration by Robertson and his co-workers<sup>24</sup> that rats and monkeys maintained for a year or more in atmospheres saturated with the vapors of propylene and triethylene glycol could thrive and bear young.

It has also been shown that no fire or explosive hazard is offered by the vapors in the concentrations required for air sterilization.<sup>3</sup>

*Effect of Glycols on Surfaces and Fabrics.* Propylene and triethylene glycol vapors are without effect upon fabrics. The vapor of propylene glycol produces tackiness on certain varnishes, but this effect has not been observed with triethylene glycol.

**Conclusions.** Though practical experience with the glycol vapors is extremely meagre, early reports encourage the hope that they may be of value in the control of infections acquired *via* the respiratory tract. Moreover, if the use of the vapors be combined with adequate dust control, a significant decrease in respiratory infection may result.

Practical engineering problems in the distribution of the vapor are being studied. The maintenance of an optimum glycol concentration in hospital wards has been shown to be practicable, especially when a regulating device or "glycolstat" is employed. The practical use of the vapors in air-conditioning systems is under investigation but has not yet been perfected.

Though the bactericidal effect of glycol vapors is important, its virucidal action may prove to be of greater practical value. Finally, it should again be emphasized, that the final practical utility of glycol vapors, or any other control measure predicated upon the reduction of the bacterial content of the air, depends upon whether a large or a small proportion of respiratory-acquired disease is air-borne. An increasing body of evidence indicates the amount of air-borne infection is greater than was formerly believed.

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## 10. RECENT STUDIES ON THE CONTROL OF DUST-BORNE BACTERIA BY TREATMENT OF FLOORS AND BEDCLOTHES WITH OIL\*†

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It is now well established that individuals ill with certain infections of the respiratory tract markedly contaminate their environment with the specific etiologic agents which may survive in dust and bedclothes for long periods of time. Diphtheria bacilli,<sup>6</sup> staphylococci,<sup>17</sup> pneumo-

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† Shortly after this report was given (May 3, 1944), three papers by English investigators<sup>15, 17</sup> appeared in the May 6th number of the *Brit. Med. J.* They contained pertinent information, relative to methods and results of controlling dust-borne infections by treatment of floors and bedclothes with oil, which has been incorporated in the present review.

cocci,<sup>4,12</sup> and tubercle bacilli<sup>23</sup> have been isolated from ward dust. The hazardous degree to which the skin, hands, wearing apparel, bedclothes and room dust can become seeded with pathogens, however, has been shown particularly in the studies of infection in wards housing patients with hemolytic streptococcal disease,<sup>7,8,13,29,36</sup> and from observations on the streptococcal output of healthy "carriers."<sup>15,16</sup>

Floor dust and bedclothes especially have been shown to harbor millions of hemolytic streptococci.<sup>21,29</sup> What part these "environmental reservoirs" of bacteria play in the spread of infections in barracks, wards, schools and homes, and so on, is not clearly established. The great rise in the bacterial count of the air in acute respiratory disease wards and barracks during bedmaking and floor sweeping has led an increasing number of observers to conclude that infections acquired *via* the respiratory tract from the inhalation of dust-borne bacteria<sup>3,7,23,29</sup> and viruses<sup>9,19,22,32</sup> are far more prevalent than generally recognized.

Ultraviolet light,<sup>20</sup> glycol vapors,<sup>25</sup> hypochlorous acid,<sup>26</sup> and so on, employed in the sterilization of air have only a limited effectiveness against dried dust-borne organisms. The development of adequate dust and lint control measures, therefore, as a means of preventing the dissemination of pathogens through the air becomes of great importance. The application of oil to floors and bedclothes for the purpose of holding dust, lint and bacteria have been found to be highly effective. Studies concerning the application and results of these methods are given in this report.

**Oiling Floors.** *Kind of Oil.* The specifications of the crude paraffin oil (spindle oil) used by the English investigators<sup>28</sup> and of the pale paraffin oil employed by the Commission on Air-Borne Infections<sup>5,27</sup> are essentially similar. Both meet the U. S. Government specifications,<sup>11</sup> which require that the flash point (open cup) shall be 300° F. or more; the viscosity at 100° F., 70 to 110 seconds; a pour point not higher than 30° F.; and a pale lemon color. The general requirements of floor oil are that it shall be clear, well refined, petroleum-oil, free from sediments and foreign material and have no objectionable odor.

*Amount of Oil Required.* The amounts of oil necessary to hold dust and lint depends chiefly on the kind of floor and the duration of effectiveness desired. As little as 1 gallon of oil applied per 1000 sq. ft. of wooden floor surface is sufficient to hold dust for a few days.<sup>28</sup> Such small amounts initially applied require oiling every 2 or 3 weeks. The duration of effectiveness of the floors to hold dust, lint and bacteria increases with each application.<sup>28</sup> Unfinished soft and hardwood floors can take as much as 1 gallon of oil per 150 sq. ft. The dust-holding effectiveness of such a single, large, initial application lasts for as long as 6 months, provided the floors are mopped only with warm water and not too frequently.<sup>5</sup> In treating smooth surfaced floors, *e. g.*, composition, linoleum, varnished and waxed, the oil should be applied in small amounts in order to avoid slipperiness and must be reapplied frequently.<sup>5,28</sup>

*Application of Oil.* Before oil is applied to floors, they should be thoroughly cleaned and dried. The manner of application depends on

how much oil is to be used. For small amounts, *e. g.*, 1 gallon per 1000 sq. ft., a cloth mop is best.<sup>28</sup> For larger quantities, a hair broom is most satisfactory.<sup>5</sup> It may also be applied as a sweeping compound mixed with sawdust.<sup>5</sup> Initially oiled floors, regardless of the method of application, are at first slippery and wet. A few to several hours are required for the oil to soak into the floors.

The mechanism of the dust and bacteria holding action of floor oils is a mechanical one only, and depends on the stickiness of the oiled surface.<sup>5,28</sup> When oiled floors are swept the dust, lint, and so on mats together in increasingly larger clumps which either roll along the floor or rise only a short distance into the air.<sup>5,28</sup> Floor oils have no bactericidal action. Various antiseptics and germicides have been added to floor oils without success.<sup>33</sup>

*Control of Dust-borne Bacteria by Oiling Floors Alone.* Van den Ende, Lush and Edward, 1940, were the first to call attention to the dust and bacteria holding properties of crude paraffin oil (spindle oil).<sup>33</sup> They carried out an experiment in which they beat blankets artificially seeded with hemolytic streptococci in two comparable rooms, one with an oiled and the other with an untreated floor. After allowing time for the bacteria to settle, blood agar plates were placed in each room and the floors were swept. The resulting collection of streptococci on the plates showed a marked reduction (89%) in the aerial contamination of the room with the oiled floor. Thomas<sup>28</sup> extended these observations to army canteens and hospital wards. Using the Bourdillon, Lidwell and Thomas "slit sampler" and sampling 10 cu. ft. of air he found that a single application of spindle oil (1 gallon for 1000 sq. ft.) to floors resulted in a striking and continuous reduction (80 %) for 10 days in the number of bacteria projected into the air during sweeping. Similar observations were made during dust control studies in hospital wards by the U. S. Naval Medical Research Unit No. 1.<sup>24</sup>

Crosbie and Wright<sup>6</sup> greatly reduced the air contamination with diphtheria bacilli by oiling the ward floors. Robertson and associates,<sup>27</sup> studying the effect of oiling floors on the bacterial content of barracks' air, observed a 70% reduction in the number of bacteria in the air in oiled floor barracks during the time the men were getting up, dressing, sweeping and making beds. Andrewes,<sup>2</sup> reviewing the methods of controlling the spread of infectious diseases in crowded public places, recommended strongly that wherever possible floors should be oiled to prevent dissemination of dust-borne pathogens.

*Control of Dust-borne Bacteria as a Means of Preventing Respiratory Infections.* Two investigations in army installations have so far been reported. Feasby and Bynoe<sup>10</sup> in Canada consider that adequate dust control measures such as good ventilation, sweeping the huts with oiled sweeping compounds by an orderly after the men had left the hut, were chiefly responsible for the reduction of respiratory tract infections among the men living in the dust controlled huts. Crowding was considered also to be a factor in the higher rate of their control group. Anderson, Buchanan and MacPartland<sup>1</sup> in England studied the control of respiratory infections by oiling floors in two army units

of approximately the same size (1300 to 1700 each) and comparable personnel, in a large training center from December, 1942, through March, 1943. Oil was applied (1 gallon per 1000 sq. ft.) to the barracks floors approximately every 4 weeks. Unit A, living in oiled floor barracks, had an average weekly respiratory infection rate of 7 per 1000 men, while in the control unit the rate was 38 per 1000 men. An outbreak of acute respiratory disease of epidemic proportions occurred in the control unit with no corresponding rise on the rate of infection in the test unit.

**Oiling Bedclothes.** *Application of Oil to Bedclothes.* The treatment of bedclothes with dust-laying oils for the purpose of reducing dust-borne infections in hospitals was first investigated by the English.<sup>2,30,31,34,35</sup> The two methods initially employed by them consisted in the impregnation of bedclothes with (1) paraffin oil dissolved in an organic solvent,<sup>2,30,31,34</sup> and (2) a special oil-in-water emulsion.<sup>35</sup> While the bedclothes treated by these two methods exhibited excellent dust and bacteria holding properties the oil preparations were, for various reasons, found to be unsatisfactory for laundering procedures. Further investigations by Harwood, Powney, and Edwards<sup>18</sup> of the British Laundry Research Association has resulted in the preparation of 2 oil-in-water emulsions which they found satisfactory for the oil treatment of bedclothes. They are as follows:

<i>For Woolen Goods</i>		<i>For Cotton Goods</i>	
	Parts by vol.		Parts by vol.
Technical mineral oil . . . . .	20	Technical mineral oil . . . . .	20
Fixanol C* . . . . .	2	Teepol† . . . . .	3
Water . . . . .	78	Water . . . . .	77

\* Fixanol C emulsion is a cation-active agent of the cetyl pyridinium bromide type.

† Teepol is an anion-active agent based on the sodium salts of sulfated secondary alcohols.

The application of the oil to the bedclothes takes place as the final rinse after washing. As these emulsions are designed to cause a selective absorption of the oil by the blankets and bedclothes, the amount to be added to the laundry wheel is calculated on the percentage of oil desired in them. The quantity of oil recommended is enough to give 5% dry weight in the bedclothes. Analysis of blankets and cotton goods treated with such solutions actually were shown by analysis of the oil content to contain approximately this amount.

In field studies of the Commission on Air-Borne Infections\* on the prevention of respiratory infections in army barracks by treating floors and bedclothes with oil, Robertson and associates<sup>27</sup> employed an oil-in-water emulsion in 1 and 2% solutions. Its formula is as follows:

	Grams
Mineral oil (Fractol A) . . . . .	88.0
Oleic acid (purified) . . . . .	8.9
Triethanolamine . . . . .	3.9
Lecithin . . . . .	0.01

\* Board for the Investigation and Control of Influenza and Other Epidemic Diseases, U. S. Army.



The oil is applied to the blankets as the final rinse. When bedclothes, both woolen and cotton goods, are treated in an emulsion calculated to give approximately 5% maximum take up by dry weight of the bedclothes, from 1.5 to 4% oil is deposited in the blankets.

These two types of dilute water-in-oil emulsion formulæ described by the English workers<sup>18</sup> and ourselves<sup>5</sup> can be applied on a large scale under the direction of skilled help. Bedclothes, both woolen and cotton fabrics, containing from 1.5 to 5% oil by weight appear no different than unoiled ones, and do not constitute a fire hazard.<sup>27</sup>

*Control of Dust-borne Bacteria by Oil Treatment of Bedclothes.* Andrewes and his co-workers<sup>2</sup> first reported the dust-laying power of oiled bedclothes. Oiled and unoiled blanket strips were artificially infected with a coarse spray of hemolytic streptococci or staphylococci, then dried and subsequently beaten in a room, and plates exposed for 5 minutes. In the case of all-wool oiled blankets there was a 95% decrease in the number of bacteria liberated into the air. The bacterial reduction in the case of treated cotton sheets were less pronounced but significant. Van den Ende, Edward and Lush,<sup>31</sup> studying blankets containing from 2.3 to 6.5% oil, obtained a reduction of 90% in the amount of dust and numbers of bacteria which could be liberated from them by shaking. Oiled cotton goods (sheets) gave a 70% reduction. Further observations by Thomas and Van den Ende,<sup>30</sup> Van den Ende and Spooner,<sup>34</sup> and Van den Ende and Thomas<sup>35</sup> on the effect of oiled and unoiled bedclothes on the contamination of the surrounding air due to bedmaking in hospital wards, showed that oiling the bedding produced a marked reduction in the dispersion of bacteria from this source, which varied from 75 to 99% on different tests. It was found that when the bedclothes were heavily contaminated, oiling the floors had no effect on the rise in the bacterial population of the air following bedmaking.<sup>30, 34, 35</sup>

Robertson and associates<sup>27</sup> found that bedclothes, blankets, sheets, pillow cases, mattress covers, containing from 1.5 to 2.5% oil gave reductions in the total number of bacteria liberated during bedmaking of about 70%. They<sup>5</sup> also found that adequate control of dust- and lint-borne bacteria in oiling floors and bedclothes increased the effectiveness of triethylene glycol in sterilizing the ward air.

*Application of Oil to Floors and Bedclothes for the Prevention of Respiratory Tract Infections.* Wright, Cruickshank and Gunn<sup>37</sup> recently reported a 12-week study on the control of dust-borne streptococcal infections in two identical 18-bed measles wards by treating floors with spindle oil, and bedclothes with dilute oil-in-water emulsions, to give an oil content in them of approximately 5%.<sup>18</sup> Patients as far as practicable were admitted to test and control wards alternately. In the test ward for the first 3 weeks the effect of oiled floors alone was studied. The last 9 weeks oiled bedding, including blankets, counterpanes, sheets, pillow slips, patients' garments, towels, gowns, white coats, curtains and so on were used. In the control ward no dust control measures were employed.

As Type 6 streptococcus accounted for about 90% of the cross-infections it was used as the "indicator organisms." In the test ward

with oiled floors alone, the infection rate was 58.1%, compared with a rate of 53.3% in the control ward. The middle ear complications were the same, 18.4%, in each ward. Hemolytic streptococci, mostly Type 6, were numerous in the air during bedmaking. Thus, oiled floors alone were not sufficient to control dust-borne streptococci in measles wards.

During the last 9 weeks, when both oiled floors and oiled bedding were employed, the mean air count for hemolytic streptococci during bedmaking was reduced 97.5%. The mean hemolytic streptococcus count during sweeping was 99% less than in the control ward. The cross-infection rate was 18.6%, while in the control ward it rose to 73.3%. The middle ear complication rate due to Type 6 was 2.8%, compared to 14.3% in the control ward. In this study, the combined application of oil to floors and bedclothes appeared to control effectively dust-borne streptococcal infections in measles wards. However, the results were not entirely conclusive because (1) the contamination of the toys were not controlled, and (2) the petroleum jelly used in performing the nasal toilets of the children was contaminated with Type 6 streptococci.

The Commission on Air-Borne Infections<sup>5</sup> has made a study of the effect of oiling floors and bedclothes on the incidence of acute respiratory diseases in a considerable number of troops, approximately 3600 in the test and a similar number in the control barracks. The study extended over a period of 10 weeks. During this time there was an average weekly reduction of 24% in hospital admissions for respiratory diseases from the treated barracks. The reduction in hospital admissions was greatest in the test groups whose corresponding controls had a high rate of disease. Thus, where the average weekly admission rate was 30 per 1000 in the control, it was 14 per 1000 in the test groups, giving an average weekly reduction in hospital admissions of over 50%. In these groups there was also an average weekly reduction of 37% in the number of dispensary visits for respiratory infections from the test barracks.

**Conclusions.** 1. The application of oil to floors is a simple and economical procedure.

2. Methods for the oil-treatment of bedclothes on a large and practical scale have been reported. Much remains to be done in perfecting economical and stable oil-in-water emulsions and techniques of application which can be carried out by unskilled laundry workers.

3. There are now ample data to show that oiling floors and bedclothes are effective procedures for the control of dust, lint and dust-borne bacteria in the laboratory, hospital wards and barracks. Where bedclothes constitute the major source of aerial contamination, oiling the floors alone is not sufficient.

4. The studies reported to date on the control of respiratory infections by the use of these dust and lint control measures are favorable. Much additional data as to their advantages and limitations in relation to other preventative procedures are needed before their efficiency in controlling dust-borne infections can be accurately determined.

5. The combination of the oiled floors and bedding with air steriliza-

tion measures holds real promise for the ultimate control of air and dust-borne diseases.

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#### 11. SAMPLING DEVICES

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THE determination of the number of air-borne bacteria in a certain volume of air allows some insight into the effectiveness of factors which might control the spread of air-borne diseases. Direct proof for

the effectiveness of a control measure can be obtained only by the demonstration of a decrease in disease incidence involving long periods of study. On the other hand, information on bacterial populations subjected to certain control measures can be obtained in a relatively short time and under controlled conditions.

It is for this reason that sampling methods for the determination of the number of air-borne microorganisms have been worked out.<sup>1-13</sup> When by these air sampling methods a certain control measure has been found to be effective under the constant conditions of an experimental chamber in which a certain pathogen or non-pathogen has been introduced, the control measure can then be applied under field conditions and air samples again taken in order to determine whether the control measure is still effective. Epidemiologic data should, of course, be collected as a means of correlating the control measure with disease incidence.

Only under special conditions will the determination of pathogens with the help of sampling devices be possible under field conditions, because in general they represent only a small proportion of the total bacterial population. Therefore, a decrease of non-pathogens in a treated air space as compared to a control space is taken as a measure for the efficacy of the treatment.

The value of such data is determined by the validity of certain assumptions:

1. A control measure which affects most non-pathogens will also be effective on most pathogens. The factor of pathogenicity does not seem to be correlated with sensitiveness to general control measures.

2. A measure which has no effect upon non-pathogens can reasonably be assumed to be non-effective for the usual type of pathogens. When one accepts this statement, laborious and time-consuming preliminary experiments on the effect of possible control measures on pathogens can be replaced by experiments on non-pathogens following simple sampling techniques. They will enable the experimenter to decide whether a measure for controlling air-borne organisms is sufficiently promising to warrant field tests.

The determination of the number of organisms in a certain air volume is performed by samplers which follow one of two principles: impingement on solid media or atomization in liquid media.

The impinging devices which we compared are the air centrifuge, the funnel device, the slit device, the bottle device, and the sieve device. The open plate method by which organisms are collected on the media by gravity, and which we also used, can be included in this group. The atomizing methods we employed are the bead bubbler, the atomizer bubbler, and the aeroscope.

Figure 1 gives the actual number of organisms obtained with various samplers in a single experiment, and Table 1 summarizes the results of a series of similar experiments. In this table is given the number of organisms found in 10 cu. ft. of air expressed as the ratio of the number of organisms which settle in open plates exposed simultaneously for a 10-minute period.

From these and other data, it is clear that the group of atomizing devices gives bacterial counts which are 10 to 30 times higher than those of the impinging devices.

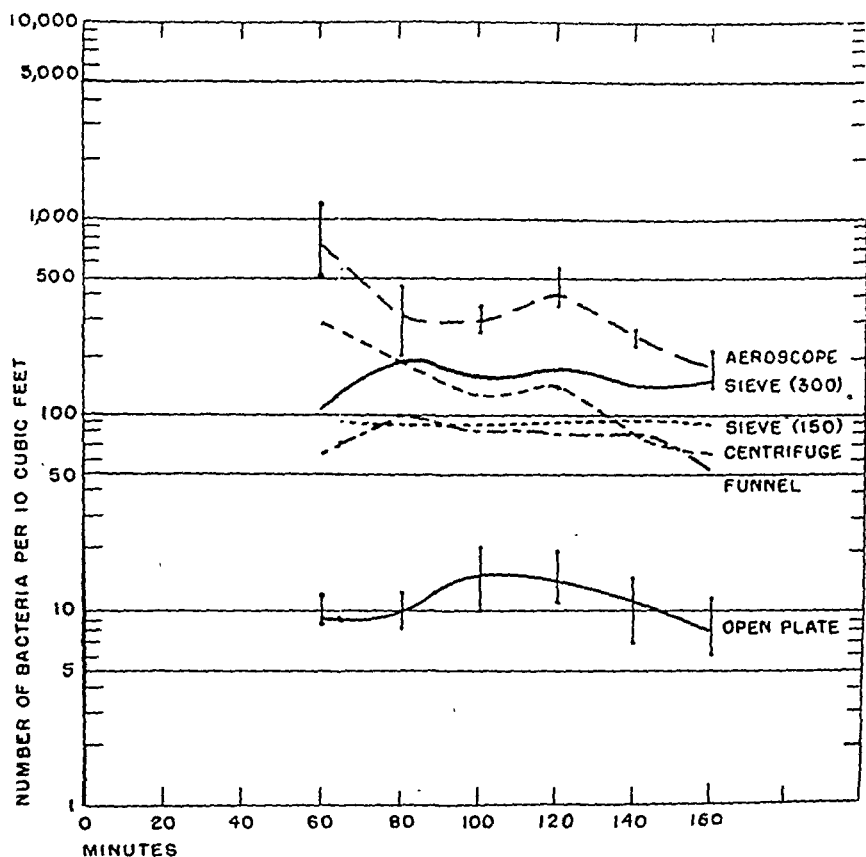


FIG. 1.—Comparison of bacterial counts of 5 sampling devices with those obtained with the open plate method (one experiment). The open plates were exposed for 10 minutes, whereas the sampling devices recorded the number of organisms in 10 cu. ft. of air. The first set of samples was taken 60 minutes after introduction of bacteria in the experimental room by means of a Graeser atomizer. The vertical lines of the aeroscope and the open plate curve indicate the numerical spread for each run. R.H. 75%, temp. 27° C. — — —, Aeroscope; —, sieve device with 300 openings in the sieve plate; ·····, sieve device with 150 openings in the sieve plate; - · - · -, air centrifuge; - - - - -, funnel device; —, open plate method.

TABLE 1.—RATIO OF BACTERIAL COUNTS OBTAINED WITH VARIOUS SAMPLING DEVICES TO THE AVERAGE COUNT OF 6 TO 10 OPEN PLATES EXPOSED AT THE TIME OF SAMPLING WITH THE DEVICES

Device	No. runs	Ratio to open plate	$\sigma$ of ratio	Coeff. of variability
Open plate . . . . .	53	1.00		
Funnel . . . . .	53	3.97	0.427	11
Bottle . . . . .	15	1.88	0.296	16
Slit . . . . .	21	1.94	0.701	36
Centrifuge . . . . .	22	2.27	0.287	13
Atom. bubbler . . . . .	18	87.07	13.160	15
Bead bubbler . . . . .	34	68.23	7.470	11

*E. coli* sprayed in room by bubbler. R.H. 35 to 55%.

It can also be seen that among the group of impinging devices and again in the groups of atomizing devices, certain samplers give con-

sistently higher bacterial counts than others in the same group, although the differences here are much less pronounced. The differences within each group have been further studied and can be related to various differences in design, leading to a more or less complete trapping of the organisms which are carried by the air.

One cause for differences in bacterial counts of samples obtained with the impinging and the atomizing devices was eliminated in our experiments but should be considered. If micro-aërobic organisms can be expected to be present in the samples, the atomizing devices will give higher counts than the impinging devices. The micro-aërobes will be submersed in the former case, when 1 cc. of the sampling liquid is plated out per Petri dish and nutrient agar is added subsequently, whereas in the impinging devices the micro-aërobic organisms are deposited on the surface of the agar, where they may not develop. In order to determine the number of micro-aërobes present, the samples obtained with the impinging device should be taken in duplicate and half of them be covered with a second layer of agar after the sampling, thus allowing the micro-aërobes to develop.

The main cause for the differences between the impinging and the atomizing devices as groups was found to be due to the fact that the air-borne microorganisms may occur in clusters. Each cluster is counted as one colony in the impinging devices, but the clumps are more or less broken up in the atomizing devices.

Results of 4 series of experiments furnish indirect proof that the breaking up of clusters is mainly responsible for the high bacterial counts obtained with the atomizing devices:

1. When bacteria are introduced in an experimental room by an air stream which bubbles through a bacterial suspension, large clusters can be expected to occur in the air. When a Graeser atomizer is used, the large clusters will be broken up before they are introduced in the room. The bacterial counts obtained show that the ratio of atomizing devices to the open plate is higher in the first case than in the second.

2. When two sampling devices are run in series, invariably the second device will give higher counts when it is an atomizing device than when it is an impinging device. This indicates that the clusters of organisms which escape the first device are broken up in the atomizing device which is used as a second device.

3. When open plates are exposed simultaneously and for the same period, those with an agar surface invariably show significantly lower counts than those with a liquid surface, especially when this liquid is atomized after the sampling.

4. When samples of air containing a dye are taken simultaneously with an atomizing device (bead bubbler) and an impinging device (sieve device), and the color is determined photometrically, the atomizing device as shown in Table 2 is only about 2 times as efficient as the impinging device, since the dye "clusters" in the impinging device contribute as much to the final color as the broken-up dye clusters in the atomizing devices. The results obtained with the bead bubbler were not materially affected by the use of 0.3% agar in the place of water.

TABLE 2.—COMPARISON OF RECOVERY OF A SPRAYED DYE BY 4 METHODS

Device	Recovered dye in mg. per liter				
Bead bubbler with 0.3% agar .	1.96	2.37	0.90	1.96	2.56
Sieve . . . . .	0.77	1.02	0.42	0.95	1.33
Bead bubbler with water . .	2.60	2.51			
Bead bubbler with 0.3% agar .	2.37	2.23			

Uranine, 20 gm. per 100 cc. meat broth, sprayed in room by Graeser atomizer and recovered by the bead bubbler and the sieve device from 6 to 10 cu. ft. of air.

From these experiments we can conclude that the difference in bacterial counts between the atomizing and the impinging devices is due mainly to the fact that bacterial clusters are broken up in the atomizing devices, giving rise to high bacterial counts, and that, on the basis of the dye experiments, these counts are only to a small degree due to a somewhat more efficient manner of air sampling by the liquid devices.

Little is known concerning the pathogenicity of air-borne microorganisms in relation to the number necessary to cause a primary infection and to the different physical forms in which they can occur, namely, in clusters or singly, in droplets or dried. These factors will certainly be different for each organism involved.

Information on the manner in which microorganisms occur in a certain air space should therefore cover the following points:

1. The total number of organisms present, whether occurring singly or in clusters. An approximation to this number is given by the atomizing devices.

2. The number of particles or droplet nuclei which contain microorganisms, either singly or in clusters, and which remain suspended in the air or are in the process of settling. This number is approximated by the impinging devices.

3. The number of particles or droplet nuclei containing microorganisms, which are heavy enough to settle through gravity. The open plate method supplies this information.

It is therefore proposed that data be obtained by methods designed to procure these three physical forms in which organisms may occur in the air. The sampling methods we believe most capable of measuring the 3 physical forms and the manner of settling of the air-borne organisms are given above, namely: (1) the open plate; (2) a representative of the atomizing methods; and (3) one of the impinging methods.

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## 12. MEASUREMENT OF AIR-BORNE INFECTION BY THE DISINFECTION OF AIR\*

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THE papers presented at this round table indicate the dominance of air-borne infections among the communicable diseases surviving sanitary control during the last half century. Before the institution of sanitation, water- and milk-borne intestinal infections dominated our mortality from communicable disease. Only in recent years has environmental control of epidemic respiratory contagion been demonstrated.<sup>1</sup> Principles of sanitary control of intestinal infection may be adapted to inherent differences in the respective media and modes of spread of infection in the development of air sanitation.

Studies of air-borne infection and sanitary air control have progressed through two stages, study of the behavior of indoor air-borne parasites and the ecologic study of these parasites and their control by disinfection. The spread through the air of infection from person to persons sharing confined atmospheres and from aggregation to aggregations by persons thus exposed, distinguishes epidemics of respiratory contagion from static outbreaks of infection ingested with accidentally contaminated water, food or milk. If outside sources of contamination are not independently maintained, explosive outbreaks of intestinal infection usually cease for want of a mechanism for propagating the cases. Respiratory contagion, on the other hand, is self-propagating, waxing like fire so long as the number of susceptible persons is sufficient to maintain the case rate, and waning when this number fails, or being dramatically interrupted when changes in the conditions of spread, such as summer ventilation, dilute the atmospheric contamination per person. If summer ventilation is sufficient to cause this inter-

\* Concluding discussion of round table on air-borne infection at the meeting of the American Society of Bacteriologists in New York on May 3, 1944.

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ruption, it is logical to presume that equivalent ventilation, however practically obtained, would be as effective in the wintertime.

The increase in atmospheric volume per susceptible, consequent upon the opening of windows in the summertime, when air-borne infections decline, probably accounts for the longer season of epidemic spread of measles and chickenpox, found by M. W. Wells<sup>2</sup> in northern latitudes, where the season of closed windows is longer. A hypothesis has been advanced that the rate of elimination of indoor air-borne infection during the winter with windows closed, equivalent to that naturally provided in the summer when the windows are open, would exceed the "threshold" sanitary ventilation required to cause respiratory epidemics to wane.

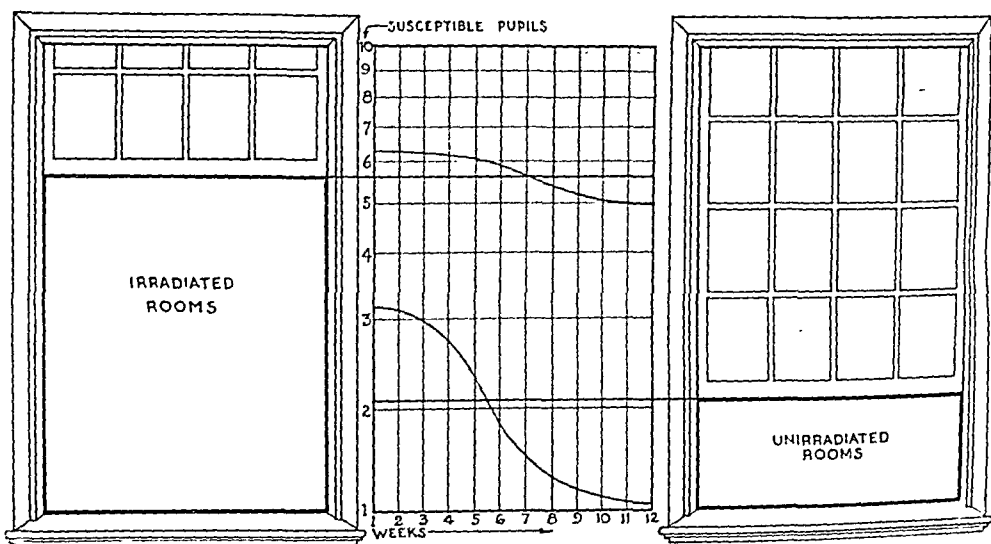


CHART 1.—Threshold sanitary ventilation.

This hypothetical relationship between sanitary ventilation and the control of spread of epidemic contagion is diagrammatically illustrated on Chart 1. The central figure shows the number of school children susceptible to measles per 300 cu. ft. of air per minute (Pennsylvania Standard for 10 pupils) in irradiated and unirradiated classrooms of the Germantown Friends School and the Swarthmore Public Schools during the 1941 epidemic. The points of inflection of the curves theoretically indicate the number of pupils provided with threshold sanitary ventilation.<sup>3</sup>

The difference in sanitary ventilation represented diagrammatically by the position of the window sashes is provided by radiant disinfection. Thus a wide open window would represent the ventilation required to prevent the epidemic spread of contagion. Actually the window in irradiated rooms should be shown wide open because the class cases were not contracted in the classrooms. The experimental measurement of "threshold" sanitary ventilation by radiant disinfection of air against epidemic spread of childhood contagion in schools is interpreted

by this dynamic hypothesis of air-borne infection to approximate 5 or 10 times normal winter ventilation.<sup>3</sup>

The hygienic interpretation of radiant disinfection into terms of equivalent ventilation requires a formulation of quantitative relationships between irradiation and disinfection. The distribution of irradiation within enclosed spaces depends upon the length of the rays, as determined by their position and direction.<sup>4</sup> Average intensity of irradiation (watts per sq. ft.), which corresponds to the concentration of disinfectant in chemical disinfection, may be determined by summing the products of radiation (watts) times length of rays (feet) between the source and the point at which the rays disappear from the atmosphere, divided by the volume of the enclosed space (cubic feet). This value, divided by the maximum uniform intensity obtainable from the radiation in a cubic space of the same volume, might be called the efficiency of irradiation.

Maximum disinfection of an enclosed space would be achieved if average intensity of irradiation were uniformly distributed throughout the entire space. In practice, however, it may not be feasible to expose occupants to the intensity required to disinfect. The amount of disinfection throughout the room, for a given average intensity of irradiation, is dependent upon circulation of the bacteria from the occupied to unoccupied zones.<sup>4</sup> The average disinfection actually achieved can be determined by bacteriologic tests, and the fraction that this represents of the maximum, which is theoretically obtainable, can be computed. This fraction might be called the efficiency of disinfection and depends *inter alia* upon the efficiency of irradiation.

The principal purpose of bacteriologic tests is to determine the average rate of removal of significant air-borne organisms from the room by sanitary ventilation. Under special circumstances, as in use of light curtains, protection may exceed the average disinfection as defined by these tests. In general, however, the concentration of organisms en route from person to person will result in less removal of organisms in the room. The efficiency of irradiation and disinfection described above may indicate the extent to which protection to the occupants differs from that indicated by the average disinfection determined by bacteriologic tests. It has been found in simplest cases, such as school-rooms,<sup>5</sup> that with low efficiency of irradiation and disinfection, higher average disinfection would be required to accomplish approximately equal protection against classroom spread of certain childhood contagions. It was therefore proposed that the hygienic rating of disinfection be raised as the indices of irradiation and disinfection efficiencies are increased by good design.

These procedures for determining dosage apply particularly to irradiation of organisms in minute particles which drift around in the air like cigarette smoke until they are breathed into the lung, vented from the room with fresh air, or destroyed by disinfection.

The school provides a favorable opportunity for study of the tactical problem of prevention of air-borne infection within an enclosed

atmosphere. Universally spread, air-borne infections are likely to be caught early in life, and if they confer lasting immunity become contagions of childhood alone. Except for brothers and sisters attending school, the normal home tends to shelter the pre-school child from exposure until it enters the school reservoir of infection. Secondary incidence may be distinguished with a high degree of probability by the clear-cut incubation period of certain childhood contagions.

The school in a small community also favors study of the strategic problem of cutting lines of communication between aggregations. Important channels of commerce in contagion within the childhood age stratum are indicated by secondary infection uncomplicated by multiple infections in the various atmospheres to which adults are exposed.

Experiments have within the epidemiologic limitations of school studies, evaluated some of the important foci of spread of air-borne contagions of childhood. A mumps epidemic at Swarthmore showed the possibility, under special circumstances, of a community epidemic among school children in spite of winter protection of the primary school. Epidemiologic analysis of secondary incidence disclosed the need, in such special cases, of extending coverage of school children beyond the school.

Germantown Friends School studies had already indicated the futility of trying to stop colds among school children by irradiating only their classrooms. These universal infections involve multiple infection in every type of aggregation, and their control requires broader coverage than does childhood contagion. The community control of upper respiratory infection, to which all ages because of temporary immunity are susceptible, will require blockade of the important channels of commerce in air-borne infection by covering the dominant foci. The public health strategy of reducing respiratory disease therefore seeks the atmospheres within which multiple infections occur and attempts to cover a major fraction of those atmospheres.

The problem may be approached experimentally by selection of large regimented groups in which exposure to unprotected atmospheres is limited. Men in military units are more exposed to each other within limited atmospheres than to men in other units, and similar opportunities may exist in civil life. It may come about, however, that the rapid growth of applied air disinfection will not wait for such studies, but will proceed to cover normal communities until the extent and importance of air-borne infection will be manifested, just as the importance of intestinal infection conveyed by water and milk was demonstrated by widespread use of water purification and milk pasteurization.

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## THE INCIDENCE OF SICKLEMIA AND SICKLE CELL ANEMIA IN 3000 CANAL ZONE EXAMINATIONS UPON NATIVES OF CENTRAL AMERICA\*

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THE incidence of sicklemia and sickle cell anemia has been determined by many investigators for most regions of the United States. Lewis,<sup>7</sup> summarizing many of these reports, reaches an over-all incidence of 7.48% sicklemia and finds that of the people showing sicklemia 2.5% will show sickle cell anemia. Archibald,<sup>2</sup> Russell and Taylor,<sup>11</sup> and Smith<sup>12,13</sup> have reported cases of sickle cell anemia from the Sudan (1 case—Arab), Gold Coast (1 case), and Nigeria (4 cases) diagnosed on the classic histologic picture of the spleens from autopsies. They give no studies of the incidence of sicklemia in their reports. Pons and Oms<sup>10</sup> found 5.29% to be present in Puerto Rico. Ortiz<sup>8</sup> reported on 7 people of one family in Puerto Rico, 3 having sickle cell anemia, and the other 4 having sicklemia. Zerbino *et al.*<sup>16</sup> reported a typical case of sickle cell anemia occurring in a 2½ year old mulatto female in Argentina; they gave no studies on the incidence of sicklemia. Weiss *et al.*<sup>15</sup> reported 2 cases of sickle cell anemia from Peru; they gave no studies on the incidence of sicklemia. In Cuba, Cabrera Calderin *et al.*,<sup>3</sup> Chediak *et al.*,<sup>4</sup> and Alonso-Patino *et al.*<sup>1</sup> have reported cases of sickle cell anemia with no studies of sicklemia. A Cuban boy with obvious negroid features, who was living in the United States, was reported by Stewart<sup>14</sup> as having sickle cell anemia. Herrick's<sup>6</sup> original classic description of sickle cell anemia was on a young negro male, studying in Chicago, who was born in the British West Indies. Pawan<sup>9</sup> reported a case of sickle cell anemia from Trinidad, B.W.I., in a male mulatto, and remarks that although no studies of the incidence of sicklemia were made, "in the course of routine blood examinations for malarial parasites and the Widal test, sickle cells have been seen, which is not surprising in a population with a high percentage of negro blood."

There have been no reports of sickle cell anemia or sicklemia from the Canal Zone or the Republic of Panama, and it is the purpose of this paper to report the incidence of sicklemia and sickle cell anemia in this region, based upon autopsy, hospital and native village studies.

**Material.** The material for this study was obtained from three sources. Since 1935 in the Board of Health Laboratory a routine procedure at the autopsy of all mestizo, brown and black people has been the preparation of petrolatum-sealed wet blood films. These films are kept at room temperature and examined for "sickling" by either the intern or resident on the Pathology Service after 24 and 48 hours. All preparations that are questionable or positive for sickled erythrocytes are examined by the pathologist for the final decision. It is therefore possible that in a few cases sickled cells may have

\* Read in part at the 442nd meeting of the Medical Association of the Isthmian Canal Zone, Sept. 21, 1943.

been overlooked, but we can be sure that all cases designated as showing "sickle cells" are reliable. In all, 1595 consecutive autopsy specimens of blood were examined in which the data and the conditions necessary for this study were suitable.

The second source of material was made possible through the kindness of Dr. H. C. Clark\* and his associates in allowing and assisting me in the collection of 628 sealed wet blood films from the villages used in his malaria control program. These specimens were examined by me after 24 and 48 hours. The third source of material is from the examination of 777 mestizo, brown and black admissions to the wards of Gorgas Hospital. The collection of this material has extended over a period of 6 months, with the sealed wet blood films also being examined by me after 24 and 48 hours.†

It has been impossible in the hospital and native population groups to determine with any degree of accuracy the racial grouping. However, in the autopsy cases the race could be determined accurately from the information upon the death certificate. In none of the autopsy cases was an attempt made to determine the race by color, facial appearance, name and so on. The information taken from the death certificate is filled out from official Canal Zone records in the majority of instances and by Panamanian officials in the other instances. The classification as to race in the autopsy series was achieved in the following manner: A person born of parents born in the British West Indies is considered a British West Indian, whether born in the Republic of Panama or in the British West Indies; this same procedure is true in all of the racial tabulations in Tables 1, 2 and 3. In the mixtures, the parents were born in the respective countries listed, irrespective of where the child was born. Thus, for example, a child born in the Republic of Panama of a father who was born in the Republic of Panama and a mother who was born in the British West Indies is regarded as a mixture of the British West Indian and Panamanian races.

In Table 1 is given the racial distributions of 1595 autopsy cases examined for the presence of sickled erythrocytes. Of the 1595 examinations, 154 (9.6%) showed sickled cells in proportions ranging from 5 to 100% of the preparation. The total numbers examined in all but the first two groups, namely, the British West Indians and the Panamanians, are too few for use in drawing conclusions. However, it is of interest to note the presence of sicklemia in Colombians, in British West Indian-Panamanian mixtures, in Colombian-Panamanian mixtures and in British Hondurians. The very finding of 2 United States negroes showing sickled cells in a total of 4 examined is ample warning against drawing any further conclusions from these smaller groups.

In Table 2 the 998 British West Indians and the 372 Panamanians examined are broken down into race-sex-age and sickled-nonsickled groups. It is apparent that there are no great differences between the British West Indians and the Panamanians. The over-all incidence of sicklemia (10%) in the combined group is comparable with the higher figures of the many studies reported from the United States ranging as they do from 4.3 to 15%.<sup>7</sup> In this study we find a consistently higher percentage incidence in females as compared to

\* A complete description of the villages is given in one of the papers dealing with malaria control methods.<sup>5</sup>

† The autopsy series of blood examinations reported here was stopped when the examination of patients' blood in this hospital was started, although we still prepare routine sealed wet blood films at autopsy for examination.

males and this is borne out in the study of the native population. Likewise Pons and Oms<sup>10</sup> in their studies in Puerto Rico found a much higher incidence in females.

TABLE 1.—RACIAL DISTRIBUTION AND INCIDENCE OF SICKLED ERYTHROCYTES IN 1595 AUTOPSIES

Race	Total number examined	Number showing sickled cells	Percentage where significant
British West Indian (B.W.I.) . . . . .	998	96	9.6
Panamanian (Pan.) . . . . .	372	42	11.2
Colombian . . . . .	66	6	9.1
B.W.I. and Pan. . . . .	55	3	
Colombian and Pan. . . . .	24	1	
Salvadorian . . . . .	16	0	
British Hondurian . . . . .	11	4	
Costa Rican . . . . .	8	0	
Ecuadorian . . . . .	6	0	
Peruvian . . . . .	6	0	
United States negro . . . . .	4	2	
Costa Rican and Pan. . . . .	4	0	
Mexican and Pan. . . . .	4	0	
Cuban . . . . .	3	0	
Nicaraguan . . . . .	2	0	
Ecuadorian and Pan. . . . .	2	0	
Venezuelan . . . . .	2	0	
Chinese and Pan. . . . .	2	0	
Indian . . . . .	2	0	
African . . . . .	2	0	
Cuban and B.W.I. . . . .	1	0	
Nicaraguan and B.W.I. . . . .	1	0	
Venezuelan and Pan. . . . .	1	0	
Costa Rican and B.W.I. . . . .	1	0	
Colombian and Cuban . . . . .	1	0	
Puerto Rican . . . . .	1	0	
Totals . . . . .	1595	154	9.6

It is of interest to consider the positive cases found and the percentage of sickling according to age groups in the combined race-sex columns (see the last two columns in Table 2). It is seen that more cases of sicklemia occur in the autopsy age groups of 40 and below, although the majority of the 1370 cases are found in the age groups beyond 40 years. No appreciable differences in the causes of death could be determined between those patients showing no sicklemia and sicklemia at autopsy, except, of course, where sickle cell anemia was the cause of death. Thus, for example, the incidence of tuberculosis was no higher in the sicklemia group than in the non-sicklemia group when compared by ages.

In the 154 cases of sicklemia, 14 cases of sickle cell anemia diagnosed by the clinical history, laboratory studies, and autopsy findings were found. Thus, the incidence of sickle cell anemia in 1595 autopsies was 0.9%, and the incidence of sickle cell anemia in the sicklemia autopsies was 9%. The usual statement<sup>1</sup> is that 2.5% of all people having sicklemia will show sickle cell anemia. In Table 3 is given the race-sex-age distribution of these cases. Eight of the cases occurred in British West Indians, 6 in Panamanians; 5 were males, 9 females. The youngest case was 1 month; the oldest was 49 years.



TABLE 3.—SICKLE CELL ANEMIA IN 1595 AUTOPSIES

Age groups	British West Indians		Panamanians	
	Male	Female	Male	Female
1- 6 mos. . . . .	1	..	1	
7-12 mos. . . . .	..	..	..	1
1- 5 yrs. . . . .	..	..	2	1
6-10 yrs. . . . .	..	1		
11-20 yrs. . . . .	..	1	..	1
21-30 yrs. . . . .	..	3		
31-40 yrs. . . . .	..	1		
41-50 yrs. . . . .	1			
Totals . . . . .	2	6	3	3
	8		6	

In the native villages of the Republic of Panama (Table 4) a total of 628 sealed blood preparations satisfactory for examination were obtained. In this group were 293 males and 335 females. A total of 41 preparations showed sickled forms; 12 males and 29 females. As the total number of males and females examined are approximately even, the marked preponderance of sicklemia in females found in the autopsy group is borne out in the native population and is of significance. The incidence of sicklemia in the entire group was 6.5%. In the males it was 4.1%, and in the females, 8.6%, or double that of the males. It was impossible to obtain reliable information from any source regarding their racial origins; they are known to be intermarried in variable degrees, to British West Indians used during the construction of the Canal and others coming in before that time.

TABLE 4.—INCIDENCE OF SICKLEMIA IN NATIVE VILLAGES, REPUBLIC OF PANAMA

Name of village	Number examined	Males	Females	Showing sicklemia		
				Number	Males	Females
New San Juan . . .	154	61	93	8	2	6
Gatuncillo . . . .	38	18	20	2	0	2
Los Guacos . . . .	9	4	5	0	0	0
Agua Clara . . . .	34	20	14	2	1	1
Santa Rosa . . . .	39	21	18	8	2	6
Guayabalito . . . .	48	26	22	5	3	2
La Laguna . . . .	86	39	47	0	0	0
Mendoza . . . . .	146	79	67	4	1	3
Camaron . . . . .	74	25	49	12	3	9
Totals . . . . .	628	293	335	41	12	29

Percentage sicklemia . . . . males 4.1  
 Percentage sicklemia . . . . females 8.6  
 Percentage sicklemia, males and females 6.5

From the routine admissions of mestizo, brown and black patients to the wards of Gorgas Hospital 777 sealed wet blood films were studied. Of these, 56 (7.2%) showed sickled erythrocytes. In these 56 patients a diagnosis of sickle cell anemia was made in 2 males and 1 female, an incidence of 5.6%. In this study 700 males revealed sicklemia in 47 instances (6.7%) and 77 females in 9 instances (11%).

By combining the autopsy, native village and hospital figures, a



total of 3000 examinations (male and female) were made with 246 instances of sickled erythrocytes (8.2%) in this large series.

Tabulating according to sex, from Tables 2 and 4 and the hospital examinations, we have a total of 1956 males showing sickled cells in 142 instances (7.2%). Likewise, for females we have 819 examinations showing sickled forms in 93 instances (11.35%).

**Conclusions.** 1. The examination of 1595 sealed wet blood films obtained at autopsies on mestizo, brown and black people dying in the Canal Zone and the Republic of Panama revealed 154 instances of sickled erythrocytes (9.6%).

2. In the 154 instances of autopsy sickled cells, there were 14 cases of sickle cell anemia (9%). Sickle cell anemia was present in 5 of 83 males and 9 of 55 females showing sickled cells. The incidence of sickle cell anemia in the 1595 autopsies is 0.9%.

3. The racial distribution of the cases examined is almost entirely from Central and South America and represents the first reported study of the incidence of sicklemia and sickle cell anemia from this area.

4. In the autopsies, 96 (9.6%) of 998 British West Indians showed sickled cells. British West Indian males showed sickled cells in 8.5%; females, 12.4%.

5. In the autopsies, 42 (11.2%) of 372 Panamanians showed sickled cells. Panamanian males showed sickled cells in 8.8%; females, 15.6%.

6. In 628 preparations obtained in native villages in the Republic of Panama, 41 (6.5%) showed sickled cells. Males showed 4.1%; females, 8.6%.

7. In 777 routine admissions to Gorgas Hospital of mestizo, brown and black patients, 56 (7.2%) showed sickled erythrocytes. A diagnosis of sickle cell anemia was made in 3 instances (5.6%) of those showing sickled forms. Males showed sickled forms in 6.7%; females, 11%.

8. Combining the autopsy, native village and hospital figures, 3000 examinations were made with 246 instances of sickled cells (8.2%).

9. Tabulation according to sex reveals sickled cells in 7.2% of males and 11.35% of females.

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STUDIES OF PLASMA VOLUME IN THE HUMAN BEING  
COMPARATIVE RESULTS OF REDUCTION OF PLASMA VOLUME,  
INTRAMUSCULAR PRESSURE AND VENOUS PRESSURE  
IN SURGICAL SHOCK

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SINCE the report of the Special Investigation Committee<sup>23</sup> on Surgical Shock and Allied Conditions, during World War I, studies on plasma volume changes in human beings suffering from the effects of shock have been meagre. Our present concept of the reduced plasma volume in shock dates back to the report of the above committee. The well controlled animal experiments of Blalock and others,<sup>1</sup> showed that a reduction in plasma volume accompanies secondary shock.\* The severity of the symptoms of peripheral circulatory failure in man is considered to be proportional to the reduction of plasma volume.<sup>7</sup> However, a number of other investigators have demonstrated that the shock state is not necessarily or quantitatively related to changes in plasma volume.<sup>3,5,6,20,22</sup>

Based on the spectacular effectiveness of plasma and serum in the treatment of shock in man, is the generally accepted assumption that such treatment, and the clinical improvement that follows the use of plasma, is due to a restoration of the reduced circulating blood volume. However, actual blood volume studies and data on human beings after the administration of plasma are meagre. The paucity of such studies on plasma volume of human beings made before operation prior to the inception of postoperative depression and at the appearance of surgical shock, hence warrants the reporting of data on such studies.

**Methods.** Plasma volume determinations were made on 7 persons. These were among the group of 97 patients in whom the dynamics of the venopressor mechanism was also being studied. The sequences in the failure of the venopressor mechanism associated with the appearance of peripheral circulatory failure have been reported elsewhere.<sup>13</sup>

The plasma volume was determined by the blue dye (T-1824) method of Gregerson and Gibson.<sup>8</sup> The dye was allowed a minimum of 30 minutes for mixing and distribution after injection, and the curve of the dye disappearance was always determined. The recheck determinations were made with a fresh injection of the dye.

The concentration of the dye in the serum was determined with a Lumetron photoelectric colorimeter. This instrument which employs 2 photoelectric cells is capable of a high degree of accuracy. In our determinations, 4 to 5 cc. of plasma were used for each determination in a cell of 1 cm. thickness. The error in plasma volume determinations was 1% (25 cc. in 2500 cc. of plasma volume). The hematocrit was determined in Wintrobe tubes.<sup>25</sup> Arterial pres-

\* Surgical, hemorrhagic (oligemic, or hematogenic) shock and the delayed effects of trauma<sup>2</sup> are all grouped as secondary shock. [It should be noted, however, that "secondary shock" is often used in a more restricted sense.—Ed.]

sure was obtained with a mercury manometer. Venous and intramuscular pressure measurements were made by the gravity flow method in recumbency, previously described in an earlier article.<sup>9</sup> The error of the method has been discussed.<sup>10</sup>

TABLE 1.—POSTOPERATIVE CONVALESCENCE. APPENDECTOMY  
(Comparative Blood Volume and Venopressor Mechanism studies to Determine the Effect of Paredrine, 20 Mg. Subcutaneously)

Time	Elapsed time in min. after paredrine	Plasma vol. (cc.)	Total blood vol. (cc.)	Hematocrit (%)	Intra-muscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury	Pulse rate in beats per min.
A.M.								
8:35	..	2727	5097	46.5				
9:05	..	2727	5125	46.8				
9:16	..	..	..	..	112	14.4	118/90	86
9:32*	0	..	..	..	112	12.8	120/80	80
9:35	..	..	..	..	118	12.5	128/76	80
9:40	..	..	..	..	112	12.7	150/80	70
9:45	..	..	..	..	115	13.3	160/88	68
9:50	18	2727	5004	45.5	..	13.8	164/88	68
9:55	23	..	..	..	..	14.1	190/100	66
10:14	42	2727	4958	45.0				
11:00	88	2798	5041	44.5	118	12.8	108/68	95

C. B. Control No. 1. Group 1. There was no significant change in either the blood volume or in the venopressor mechanism.

\* Paredrine 20 mg. (H) subcutaneous.

TABLE 2.—COMPARATIVE BLOOD VOLUME AND VENOPRESSOR MECHANISM STUDIES TO DETERMINE THE EFFECT OF PAREDINE 40 MG. SUBCUTANEOUSLY

Time	Elapsed time in min. after paredrine	Plasma vol. (cc.)	Total blood vol. (cc.)	Hematocrit (%)	Intra-muscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury	Pulse rate in beats per min.
A.M.								
9:09	..	3030	5855	48.5				
9:47	..	3030	5827	48.0				
9:55	..	..	..	..	72	7.5	120/70	84
10:01*	0	..	..	..				
10:16	15	3030	..	..	64	8.6	160/82	70
10:25	24	..	..	..	63	9.4	180/110	68
10:31	30	3030	5827	48.0	61	9.6	194/112	68
10:45	44	..	..	..	66	9.0	190/112	68
11:00	59	..	..	..	60	6.0	170/105	70
11:25	84	3030	5855	48.5	56	5.8	130/72	78

J. M. Control No. 2. Group 1. There was no significant change in the blood volume. Paredrine in suitable dosage increases venous pressure but does not affect intramuscular pressure.<sup>15</sup>

\* Paredrine 40 mg. (H) subcutaneous.

**Results.** Four of the 7 persons studied were normal individuals on whom the plasma volume was determined incidental to studies on the influence of other drugs<sup>15</sup> (Tables 1 to 4). These patients, who served as controls, showed no alterations in the plasma volume, in the venous pressure, or in the intramuscular pressure during the experiment.

Three patients were studied after major surgical procedures with and without attendant loss of blood during the operation (Tables 5, 6, 7). The plasma volume figures of these 3 patients were of interest because they showed: in the 1st patient (Table 5), the features of rapidly developing surgical shock; in the 2nd (Table 6), the effect of hemorrhage and rapidly developing peripheral circulatory failure; and in the 3rd (Table 7), the effect of surgical operation without undue loss of blood and with a minimal of postoperative depression.

TABLE 3.—COMPARATIVE BLOOD VOLUME AND VENOPRESSOR MECHANISM STUDIES TO DETERMINE THE EFFECT OF PAREDINE 30 MG. SUBCUTANEOUSLY

Time	Elapsed time in min. after paredrine	Plasma vol. (cc.)	Total blood vol. (cc.)	Hematocrit (%)	Intramuscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury	Pulse rate in beats per min.
A.M.								
8:06	..	2655	5206	49.0				
8:36	..	2655	5009	47.0				
8:56	..	2655	5310	50.0				
9:15	..	..	..	..	89	9.8	120/70	80
9:20*	0	..	..	..				
9:25	5	..	..	..	88	9.9	200/110	50
9:30	10	2655	5474	51.5	94	15.1	210/110	50
9:40	15	..	..	..	88	14.1	220/112	68
9:45	20	2655	5533	52.0	81	13.6	200/96	76
10:06	41	..	..	..	82	11.8	185/104	72
10:45	80	..	..	..	82	10.2	150/90	76
10:55	90	2655	5310	50.0	83	10.2	156/90	72

M. Control No. 3. Group 1. There was no change in blood volume. Paredrine increases venous pressure but does not affect intramuscular pressure.<sup>15</sup>

\* Paredrine 30 mg. (H) subcutaneous.

TABLE 4.—POSTOPERATIVE CONVALESCENCE. BRODIE'S ABSCESS  
(Comparative Blood Volume and Venopressor Mechanism Studies to Determine the Effect of Nikethamide 10 Cc. Intravenously)

Time	Elapsed time after Nikethamide	Plasma vol. (cc.)	Total blood vol. (cc.)	Intramuscular pressure in mm. water	Venous pressure in cm. water
A.M.					
8:12	..	2440	4207	96	11.4
9:42*	0	..	..		
9:52	10	..	..	113	19.0
10:09	17	2440	4207	97	13.7

N. M. Control No. 4. Group 1. The blood volume remained unchanged. The venopressor mechanism was heightened, intramuscular and venous pressure both increased, after nikethamide.

\* 10 cc. Nikethamide intravenously.

The patient in Table 5 showed all the clinical features of surgical shock immediately following a cholecystectomy. A small quantity of blood was lost during the operation. There was *no change in the plasma volume when clinical shock was evident*. The intramuscular pressure, however, showed a marked decrease. Any considerable reduction in the plasma volume did not occur until late in the course of events, 10 hours 3 minutes after the operation. Peripheral circulatory failure

TABLE 5.—CHOLECYSTECTOMY. STORMY POSTOPERATIVE COURSE WITH EARLY APPEARANCE OF SURGICAL SHOCK (Comparative Blood Volume and Venopressor Mechanism Studies. Demonstrating the Failure of the Venopressor Mechanism in Surgical Shock, and Its Treatment With Nikethamide)

Time	Elapsed time in min. from beginning of operation	Elapsed time postoperative	Plasma vol. (cc.)	Decrease in plasma vol. (cc.)	Total blood vol. (cc.)	Decrease in total blood vol. (cc.)	Hemato- crit (%)	Intra- muscular pressure in mm. water	Change in intra- muscular pressure in mm. water	Venous pressure in cm. water	Change in venous pressure in cm. water	Arterial pressure in mm. mercury	Remarks
A.M.													
7:15	..	..	2480	..	4350	..	43.0	..	..	..	..	..	First dye injected
7:46	..	..	..	..	..	..	..	..	..	..	..	..	Anesthesia
8:55	0	..	..	..	..	..	..	77	..	14.4	..	..	5% glucose I.V. 10:30 A.M.
9:03	132	..	..	..	..	..	..	25	(-)52	7.5	(-)6.9	75/50	Operation finished; patient in shock
11:15	144	0	2460	(-)20	4300	(-)50	..	..	..	..	..	..	
11:37													
P.M.													
12:00	..	..	..	..	..	..	42.8	33	..	6.9	(-)7.5	..	Nikethamide, 10 cc. I.V.
12:42	..	1 hr. 9 min.	..	..	..	..	43.0	..	..	7.7	..	..	
12:46	..	..	..	..	..	..	..	95	(+)70	13.9	(+)7.0	..	Clin. impr. evident
12:50	..	1 hr. 33 min.	2392	(-)88	4200	(-)150	43.0	92	..	9.0	..	85/54	700 cc. glucose between 1 and 2:30 P.M.
1:00	..	..	..	..	..	..	..	56	..	..	..	98/60	Pulse 132; signs of shock
2:30	..	..	..	..	..	..	..	..	..	..	..	..	
8:23	..	8 hrs. 46 min.	2239	(-)241	4070	(-)280	45.0	55	(-)40	4.4	(-)9.5	..	Nikethamide, 5 cc. I.V.
8:35	..	..	..	..	..	..	..	55	..	4.7	..	..	
8:55	..	..	..	..	..	..	..	41	(-)54	4.3	(-)9.6	..	
9:20	..	..	..	..	..	..	..	..	..	..	..	100/68	Clinically improved; symp-
9:24	..	..	..	..	..	..	..	75	(+)34	10.1	(+)5.8	96/60	toms of P.O. depression
9:29	..	..	..	..	..	..	..	75	..	7.6	..	94/64	with adequate peripheral circulation
9:40	..	10 hrs. 3 min.	2064	(-)416	3621	(-)729	42.8	80	..	6.0	..	..	Condition satisfactory
A.M.													
9:10*	..	..	..	..	..	..	..	51	..	5.4	..	..	

*Surgical shock was clinically evident with no change in plasma volume. Intramuscular pressure, however, showed a marked drop early in the course of events. The maximum decrease in intramuscular pressure coincided each time with the appearance of peripheral circulatory failure. Clinical improvement coincided with the heightening of the venopressor mechanism after the use of Nikethamide. Clinical improvement was obtained after Nikethamide despite the loss of at least 416 cc. of plasma volume. The clinical course coincided with the direction of the changes in intramuscular pressure, rather than with the alterations in plasma volume.*

\* 1st P.O. day.

TABLE 6.—HYSTERECTOMY. LARGE LOSS OF TOTAL BLOOD VOLUME FROM HEMORRHAGE DURING THE OPERATIVE PROCEDURE. RAPIDLY APPEARING SHOCK  
(Comparative Blood Volume and Venopressor Mechanism Studies. Demonstrating the Failure of the Venopressor Mechanism After Surgical Operation With Hemorrhage, and the Treatment of Shock With Nikethamide and With Blood Transfusion)

Time	Elapsed time in min. from beginning of operation	Elapsed time post-operative	Plasma vol. (cc.)	Change in plasma vol. (cc.)	Total blood vol. (cc.)	Change in total blood vol. (cc.)	Hematocrit (%)	Intra-muscular pressure in mm. water	Change in intra-muscular pressure in mm. water	Venous pressure in cm. water	Change in venous pressure in cm. water	Arterial pressure in mm. water	Remarks
A.M.													
8:45	0	..	2940	..	5250	..	44 0	96	..	6 6	..	175/94	Anesthesia, ethylene-ether
9:30	13	..	..	..	..	..	..	96	..	11.3	(+)4.7	155/105	Trendelenburg position
9:43	44	..	..	..	..	..	..	82	(-)14	27.1	(+)20 5	158/105	
10:14	47	..	2350	(-)590	4122	(-)1128	43 0	..	(-)39	15.9	(-)11.2	158/105	
10:17	60	..	..	..	4114	..	43 0	57	..	..	..	..	Transfusion of 500 cc. whole blood completed
10:30	63	..	2345	(-)323	..	(-)738	..	60	..	..	..	..	Peripheral circulatory failure evident
10:33	120	0	..	..	..	..	..	..	..	..	..	..	
11:30	..	..	2617	(+)272	4512	(+)398	42 0	40	(-)56	3.6	(-)23.5	125/70	
P.M.													
12:45	..	..	..	..	..	..	..	..	..	..	..	..	1000 cc. 5% glucose administered
2:00	..	..	..	..	..	..	..	..	..	..	..	..	400 cc. whole blood transfusion completed
4:00	..	4 hrs. 23 min.	3090	(+)745	5660	(+)1546	45.4	..	..	..	..	..	Clinical condition good
12:15*	..	..	2740	(-)200	4567	(-)683	39.5	47	..	6.5	..	138/92	Clinical condition good

Intramuscular pressure showed a significant decline early in the course of events, and preceded the appearance of peripheral circulatory failure. A loss of 590 cc. of plasma volume, and 1128 cc. of total blood volume was not accompanied by clinical signs of shock. Although intramuscular pressure was beginning to drop, the venopressor mechanism had not failed. The maximum decline in intramuscular pressure, and failure of the venopressor mechanism coincided with clinical evidences of peripheral circulatory failure. This, despite a restoration of 272 cc. of plasma volume by the use of a 500 cc. whole blood transfusion. The restoration of 745 cc. plasma volume from the use of 900 cc. whole blood transfusion, however, coincided with clinical improvement. A decrease of 200 cc. plasma volume on the 1st postoperative day was present with an adequate peripheral circulation. The venopressor mechanism was also compensated. The clinical picture of peripheral circulatory failure coincided with the failure of the venopressor mechanism rather than with the loss of plasma volume of 590 cc. A restoration of 745 cc. of plasma volume through the use of 900 cc. whole blood transfusion, coincided with improvement in the clinical picture.

\* 1st P.O. day.

was evident when the patient was examined 144 minutes after the beginning of the operation. The plasma volume figures were 2480 and 2460 cc., respectively. At 132 minutes, intramuscular pressure was measured and found to have dropped 52 mm. to a low level of 25 mm. water. Venous pressure had dropped 6.9 cm. from the compensated high level attained during the operation.

TABLE 7.—RETROPERITONEAL SURGICAL PROCEDURE. RIGHT NEPHROPEXY  
(Comparative Blood Volume and Venopressor Mechanism Studies)

Time	Plasma vol. (cc.)	Decrease in plasma (cc.)	Total blood vol. (cc.)	Hema- tocrit (%)	Intra- muscular pressure in mm. water	Venous pressure in cm. water	Arterial pressure in mm. mercury
A.M.							
7:30*	3000	..	5357	44.0	67	5.8	110/80
10:50†	..	..	5480	..	60	5.8	
11:34‡	2795	(-) 205	5480	49.0§	60	5.8	

Retroperitoneal operations show a minimal of postoperative depression.<sup>14</sup> Despite a loss of 205 cc. of plasma volume, the clinical condition of the patient was good and there was no evidence of peripheral circulatory failure. Intramuscular pressure remained unchanged before, during and after the operation. The venopressor mechanism did not fail.

\* Preoperative.

† At end of operation.

‡ 44 minutes after operation. Clinical condition good. No evidence of inadequacy of the peripheral circulation.

§ Possible error in hematocrit?

Uncompensated peripheral circulatory failure was still evident 69 minutes after operation when Nikethamide\* (10 cc.) was given intravenously. Clinical improvement followed, and was accompanied by an increase in intramuscular pressure to 95 mm., and of venous pressure to 13.9 mm. water. The peripheral circulation was still compensated at 93 minutes (postoperative) when the plasma volume was found to be 2392 cc., 88 cc. less than the preoperative level. Intramuscular pressure was now 92 mm., and venous pressure 9 cm. water. The patient's condition was satisfactory.

The clinical condition of the patient gradually deteriorated, and 8 hours and 46 minutes after the operation he again showed the signs of peripheral circulatory failure. The plasma volume had now dropped 241 cc. below the preoperative level. Intramuscular pressure had fallen 40 mm., to 55 mm. water, and venous pressure 9.5 cm. from the heightened level attained after the administration of 10 cc. of Nikethamide 8 hours earlier, to the absolute value of 4.4 cm. water. At this point, Nikethamide (5 cc. intravenously) was again given to be followed by clinical improvement for a second time. The intramuscular pressure increased to 75 mm. and venous pressure to 10.1 cm. water, a rise of 34 mm. and 5.8 cm., respectively, from the low levels of the last previous observation. Twenty minutes later the plasma volume was 2064 cc., a decrease of 416 cc. since the operative pro-

\* Coramine-Ciba (brand of Nikethamide) was used throughout our studies.

cedure; intramuscular pressure was 80 mm. and venous pressure 6 cm. water. The clinical condition of the patient was good despite the reduction of 416 cc. in plasma volume.

The maximum reduction in plasma volume occurred 10 hours and 3 minutes after surgical shock was first manifested. The plasma loss was 416 cc., yet the clinical condition of the patient was that of the usual postoperative depression with a compensated peripheral circulation. His condition was considered satisfactory. Clinically, the situation was now no different from that commonly seen in other patients after operation who demonstrated only the usual loss of vitality and weakness without failure of the peripheral circulation.<sup>14</sup>

The patient in Table 6 showed an early decline in the plasma volume. In 47 minutes from the beginning of the operation the total volume had declined from 5250 to 4122 cc., and the plasma volume from 2940 to 2350 cc., a decrease, respectively, of 1128 and 590 cc. Despite this loss of blood, the condition of the patient was still good. The intramuscular pressure was 82 mm. water, still within the normal range, but had decreased significantly from the preoperative level. An increase in venous pressure to 11.3 cm. water was found 13 minutes after anesthesia. In the Trendelenburg (head down position) at 47 minutes, venous pressure was recorded at 27.1 cm. water. Following a transfusion of whole blood, the plasma volume increased 272 cc. At 127 minutes after operation, failure of the peripheral circulation was unmistakable despite this increase of plasma volume. The patient was in shock. Arterial pressure had dropped 50 mm. mercury, intramuscular pressure 56 mm. water, and venous pressure 23.5 cm., from the heightened level previously attained in the head down position. The increase in plasma volume did not prevent the appearance of circulatory failure, which in turn coincided with the lowest points reached by intramuscular and venous pressure. It is significant that *intramuscular pressure declined 16 minutes before the venous pressure*.

Following a second transfusion of whole blood, the total and plasma volumes were increased to preoperative levels at 4½ hours after the operation, and the clinical condition of the patient was satisfactory.

The next day, a fresh injection of the dye showed the plasma volume to be 200 cc. less than the preoperative value. Intramuscular and venous pressures had increased above the lowest points of the previous day, and were within a physiologic range. The patient showed the usual 1st day postoperative depression of vitality. Paradoxically, although the plasma volume was reduced, the clinical condition was good and there was no evidence of peripheral circulatory failure. The patient proceeded to make an uneventful recovery without further treatment for shock.

The patient shown in Table 7 underwent a right nephropexy operation. Forty-four minutes after the operation he showed a loss of plasma volume of 205 cc. Despite the reduction in plasma volume, his clinical condition was excellent and he showed no signs of peripheral circulatory failure, and little of the loss of vitality seen in the postoperative state.



*The intramuscular and venous pressures did not change from the pre-operative level.\**

**Discussion.** These findings on plasma volume came as a complete surprise to us. Our concept of the relation of the loss of plasma volume to the clinical manifestations of peripheral circulatory failure in man is based largely on studies carried over to human beings from animal experiments, chiefly in the dog. It can be safely said that a reduction in the circulating volume of plasma in both the dog and in the human being is one of the significant and constant features to be found *late* in the course of progressively developing shock.

Much confusion has been engendered as to the cause of the conditions found in the course of well developed shock in the human being, through the failure to study these on man himself. Wiggers<sup>24</sup> has repeatedly emphasized the hazards of transferring the results of animal experiments to man. There can be little doubt that the earliest phenomenon in traumatic shock in dogs is a reduction in blood volume. But this need not be so in human beings.

It appears from our study that a reduction in plasma volume need not be an early change, or an initiating factor in surgical shock or in shock following hemorrhage and surgical operation in the human being; that peripheral circulatory failure can be evident without any reduction in plasma volume; and that a certain degree of decrease in plasma volume can exist without producing circulatory failure. It is also evident that a reduction in plasma volume will be found late in surgical shock.

We are in a sad state of ignorance as to the factors which lead to the inception and production of peripheral circulatory failure in man. Part of this may be due to the failure to study adequately the dynamic factors of the peripheral circulation in the human being. All attention until recently has been focused on the reduced plasma volume and on treatment aimed at the restoration of blood volume. It is even questionable whether the well deserved popularity of human plasma in the treatment of shock is effected through a restoration of lost blood volume beyond that which the volume of plasma given adds to the circulation. Human plasma however, has a marked pressor effect on intramuscular pressure.<sup>10</sup> It seems proper to review at this point some of the known facts of the dynamics of the peripheral circulation as related to changes in intramuscular pressure in man.

A marked drop in intramuscular pressure, which reached its maximum within the 6th to 12th postoperative hour, was consistently found after surgical procedures.<sup>11</sup> Uninterrupted serial readings of intramuscular and venous pressure made during and after operation and to the development of surgical shock have been reported.<sup>12,14</sup> The earliest and first phenomenon noted either during operation or preceding the onset of surgical shock was *a decline in the level of intramuscular pressure*. This occurred from 20 to 60 minutes, usually at 45 minutes, after the operation was begun. The decline in venous

\* During our investigations, retroperitoneal operations showed the least postoperative depression or alterations in intramuscular pressure.<sup>14</sup>

pressure always followed that of the intramuscular pressure by from 16 to 50 minutes. The former time was noted in rapidly developing shock which happened on the operation table. The fall in venous pressure was noted 32 minutes before the signs of peripheral circulatory failure appeared. During the usual operative procedure, the initial decline of venous pressure followed that of intramuscular pressure within an interval of 50 minutes. The lowest points attained by intramuscular and venous pressure occurred after the initial decrease, and coincided with the appearance of peripheral circulatory failure. This was true whether or not the pressures dropped rapidly or were delayed, and the symptoms and signs of shock appeared early or late. Those patients who showed only a severe depression after operation, subtly developed peripheral circulatory failure between the 6th and 12th postoperative hour, when it was noted that intramuscular and venous pressures had coincidentally attained their maximum point of decline. The peripheral circulation immediately after operation appeared adequate, but subsequently the clinical picture became indistinguishable from that seen in those who developed shock rapidly. In both instances venous pressure as low as 1 cm. water and intramuscular pressure down to 18 mm. water have been recorded.

The lowest level to which intramuscular pressure falls in shock and before death is 18 mm. water.<sup>13\*</sup> The resistance of the muscle mass to the injection of saline does not decrease below this pressure immediately after cessation of the heart beat and of the circulation in clinical death in the human being and in the frog (*Rana pipiens*). *An intramuscular pressure of 20 mm. water in the resting muscle represents a complete absence of muscle tonus.*†

The alterations in intramuscular and venous pressure noted above in the review of the dynamics of the venopressor mechanism during and after operation, showed a constant coincidence between: (1) the loss of muscle tonus, (2) then of venous pressure, and (3) the appearance of peripheral circulatory failure.

These phenomena were also seen in both patients in Tables 5 and 6. In the one, intramuscular pressure was found to have fallen to a low level 132 minutes from the beginning of the operation, when shock

\* The range of variation was 18 to 24 mm. water (actually 18 to 24 mm. normal saline). Because of the possible variant in the method of measurement of intramuscular pressure, we regard 20 mm. water as the level of intramuscular pressure during life which represents a complete absence of the property of living muscle called tonus.<sup>13</sup>

† This is the level of intramuscular pressure found in death<sup>13</sup> when muscle tonus has disappeared.<sup>16</sup> During life, the isometric contractions of discrete muscle bundles, in the muscle at rest, serves as a microscopic pump to propel venous blood to the heart. The tonic activity of the great mass of skeletal muscle of the body thus constitutes a venous pump, just as important to the circulation as is the heart itself.<sup>18</sup> The loss of muscle tonus spells failure of the peripheral circulation just as surely as does left ventricular failure for the arterial circulation, and for the circulation at large. When the measurement of intramuscular pressure (which is a measurement of muscle tonus during life) indicates a level wherein tonic activity is practically non-existent, the forces which constitute the venous pump are no longer active. The peripheral circulation must decompenstate when intramuscular pressure fails and the venopressor mechanism becomes inefficient.

The vascularity (the number of open capillaries and venules) in a muscle is related to the number of discrete muscle bundles in contraction at any given moment.<sup>21</sup> In

was first evident. An intramuscular pressure of 25 mm. water, showing practically a complete absence of muscle tonus, was found at this time. There was no change in the plasma volume even though peripheral circulatory failure was obvious.

During the 10-hour period that plasma volume progressively declined, the peripheral circulation twice showed clinical signs of failure, and was twice restored and compensated after the administration of Nikethamide. The changing condition of the patient corresponded to the direction of the changes in intramuscular pressure, and not to those in the plasma volume.

In the second patient (Table 6), sufficient interval observations were obtained to show the decrease in intramuscular pressure, preceding that of the venous pressure. In both patients, the maximum decline in intramuscular and venous pressure for each episode coincided with the onset of peripheral circulatory failure and not with the moment of the maximum decrease in the plasma volume. Compensation of the peripheral circulation which occurred twice after the use of Nikethamide in patients (Table 5) and for each spontaneously on the first postoperative morning, coincided with an increase in intramuscular pressure from a low level to above 40 mm. water. Clinical improvement was evident despite lowered values for plasma volume.

Other studies<sup>10</sup> have shown that plasma has a most remarkable pressor action on intramuscular pressure. Just as decreasing increments of intramuscular pressure preceded a loss of venous pressure and of the appearance of peripheral circulatory failure, studies on the effect of human plasma showed that increasing increments of intramuscular pressure preceded a rise in venous pressure. Rising increments of intramuscular pressure precedes a restoration of a failed circulation. Intramuscular pressure values below 40 mm. water, when increased above this value, were found to be followed by clinical improvement and a heightening of the venous pressure to within the normal. These phenomena were also noted in this study.

The absolute increments of intramuscular pressure are not diagnostic or prognostic in the shock syndrome, except when intramuscular pres-

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tetanic contraction, the muscle is gorged with blood. During rest, there are always a number of discrete muscle bundles in isometric contraction, open capillaries and venules, and a flow of blood. *When tonic activity has ceased, there should be no blood flowing through the muscle.* Evidence for this is furnished by observations at the autopsy table and on shock that occurred during a surgical operation (L. G.). In death from shock due to explosive missiles, the biceps and abdominal muscles were bloodless and so dry that they literally cracked when cut. In surgical shock during an abdominal operation, the cut surfaces of the abdominal rectus muscle did not ooze blood as ordinarily occurred in patients in good condition under anesthesia.

In death from traumatic shock, the muscles possessed no tonus and were bloodless. Similarly, when intramuscular pressure during life had fallen during surgical shock to the level that likewise indicated an absence of muscle tonus, blood no longer flowed from the cut muscle. On the other hand, after a restoration of muscle tonus in surgical shock, empty veins became full and venous pressure rose, indicating a reestablishment of peripheral blood flow. In the muscle in death, and in the living muscle during shock, an important force that contributed to the mechanism of the venous pump, *muscle tonus*, was no longer present. The failure of the venopressor mechanism and cessation of the peripheral circulation occurred together.

sure has not changed from the normal preoperative level. We have never seen the clinical picture of shock in patients whose intramuscular pressure remained at the preoperative value, nor have we ever observed patients with peripheral circulatory failure on whom measurements of intramuscular pressure did not show either a decline from a previously recorded figure or an absolutely low level. It is the relative loss of the pressure of the muscles from a high to a lower level that appears to be an important factor in the loss of venous pressure and the appearance of the peripheral circulatory failure that follows. Likewise it is the relative fall in venous pressure from a high to a lower level that precedes the appearance of circulatory failure. This fits in with the findings of Holt,<sup>19</sup> who showed that venoconstriction may maintain peripheral venous pressure as measured in the antecubital vein in the face of a marked fall in venous pressure in the auricle. Any observed fall in venous pressure at the periphery, as from a compensated high level to a lower one *must* reflect a considerable decrease in central or auricular pressure and of venous flow. Henderson<sup>17</sup> also stressed the significance of a relative drop in venous pressure in the head-down position as an indication of a failing venous return. In this position, the blood returning from the tissues is, so to speak, poured into the great veins near the heart (the preventricular reservoir of von Recklinghausen). A falling venous pressure in this position indicates a lessened flow of blood to the preventricular reservoir. The rapid decline in venous pressure from a compensated high level during operation was seen in both patients in Tables 5 and 6 preceding the onset of peripheral circulatory failure. In one it occurred while the patient was still in the head-down position.

Intramuscular pressure values within the normal range are always associated with venous pressures within the normal range. We have never witnessed a marked drop in venous pressure with a normal or a high intramuscular pressure, nor have we observed a low venous pressure without a low intramuscular pressure.

Henderson<sup>17</sup> stoutly championed the idea that venous flow cannot be maintained and blood returned to the heart without a secondary or booster pump within the venous side of the circulation. The action of the diaphragm and the abdominal muscles, and the negative intrapleural pressure have long been recognized as factors that maintain and assist in the flow of blood to the auricle. These, plus the energy of intramuscular pressure, are the forces that constitute the venous pump. Of these, intramuscular pressure, or the intrinsic pressure and tonic activity within the muscles, is the factor of fundamental importance. It is the efficiency of the venous pump, *i. e.*, the presence or absence of muscle tonus that determines whether or not the peripheral circulation will come to a standstill, rather than changes in circulating volume. This, he has pointed out, is the mode of death in shock.

Our studies indicate that: (1) Within certain limits, a considerable reduction of circulating blood volume is compatible with an efficient venous circulation, providing that intramuscular pressure, one of the forces important in the dynamics of the peripheral circulation, is held

at an adequate level. (2) A physiologically effective venopressor mechanism coincided with an adequate peripheral circulation; one that has failed, with the appearance of surgical shock. (3) A normal peripheral circulation coincided with a normal and unchanged level of intramuscular pressure, even in the presence of a reduced plasma volume. (4) Human plasma has a decided pressor action on intramuscular pressure. (5) Nikethamide also has a marked pressor action on intramuscular pressure. The pressor action of plasma is slow, requiring 70 to 100 minutes, and the administration of 750 cc. before its pharmacologic action becomes manifest. The effect of Nikethamide, on the other hand, is very rapid. It likewise heightens the venopressor mechanism, but within 5 to 10 minutes after its administration in doses of 5 to 10 cc. intravenously, as contrasted to the 70 to 100 minutes required for plasma. (6) The presence or absence of the dynamic factors of the venous circulation (first, the relative levels of intramuscular pressure, and later that of venous pressure) corresponded more closely to the appearance or regression of peripheral circulatory failure than did changes in the plasma volume of less than 590 cc. (approximately 2 units of plasma).

The chief lesson to be derived from our studies is that greater emphasis must be placed on investigations of the dynamics of the peripheral circulation rather than upon the volume of blood that is available for the circulation, and this must be done at the bedside.

**Summary and Conclusions.** 1. Peripheral circulatory failure in surgical shock may be evident with a normal and unchanged plasma volume.

2. A decrease in plasma volume up to 590 cc. is not necessarily followed by peripheral circulatory failure.

3. Change in the clinical condition of the patient, for the worse or for the better, and the presence or absence of peripheral circulatory failure, coincide more closely with decline of, or the heightening of, intramuscular pressure, than with changes in the plasma volume.

4. Peripheral circulatory failure may be manifest with a normal or with a decreased plasma volume, but not with an unchanged intramuscular pressure, which remains in the normal range. The circulatory failure is always associated with a lowered level of intramuscular pressure.

5. An inadequate peripheral circulation, despite a plasma volume decrease of at least 416 cc., can be compensated and returned to adequacy with the restoration of a low intramuscular pressure to a higher level by the use of Nikethamide.

6. Changing increments of intramuscular pressure are an important factor in the dynamics of the peripheral circulation.

7. The kinetics of the peripheral circulation as related to intramuscular pressure (the venopressor mechanism) and other forces that may constitute the venous pump in man, are worthy of greater attention in investigations of the problem of shock; these studies must be made on the human being, preferably, rather than on other animals.

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## ABERRANT ATRIO-VENTRICULAR CONDUCTION IN A CASE SHOWING A SHORT P-R INTERVAL AND AN ABNORMAL BUT NOT PROLONGED QRS COMPLEX\*

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THE recent cardiologic literature displays considerable interest in the subject of the Wolff-Parkinson-White syndrome. This is largely due to the physiologic considerations involved. Of the various contributions to the subject 2 are outstanding: (1) Butterworth and Poindexter—on the experimental production of the syndrome of apparent bundle branch block with short P-R interval,<sup>1</sup> and (2) Wood, Wolfert and Geckeler<sup>7</sup>—who furnished histologic proof of the existence of accessory conduction connections between the auricles and the ventricles of a patient with this type of electrocardiographic abnor-

\* Read at the May meeting of the New York Heart Association.

malinity.<sup>1</sup> The original hypothesis to explain the mechanism of this syndrome as advanced by Holzman and Scherf<sup>4</sup> and Wolferth and Wood<sup>5</sup> is as follows: some hearts possess, in addition to the normal conduction system, an aberrant pathway connecting one of the auricles with one of the ventricles; through this aberrant pathway early stimulation of one of the ventricles is achieved; the spread of excitation to the other ventricle is the cause of the prolonged QRS complex.

In a recent paper, Fox, Travell and Molofsky<sup>2</sup> presented a case of Wolff-Parkinson-White syndrome in which the abnormally wide QRS complex could be *further* widened by the administration to the patient of drugs with cholinergic properties, and *narrowed* considerably by the use of atropine sulfate. It was thus shown that the QRS complex in this syndrome is not necessarily a stable structure, and that its duration could be influenced by providing more "vagus substance" or by inhibiting the functional activity of this substance.

A further step in the study of this syndrome was afforded by a case recently observed at the Hospital for Joint Diseases.

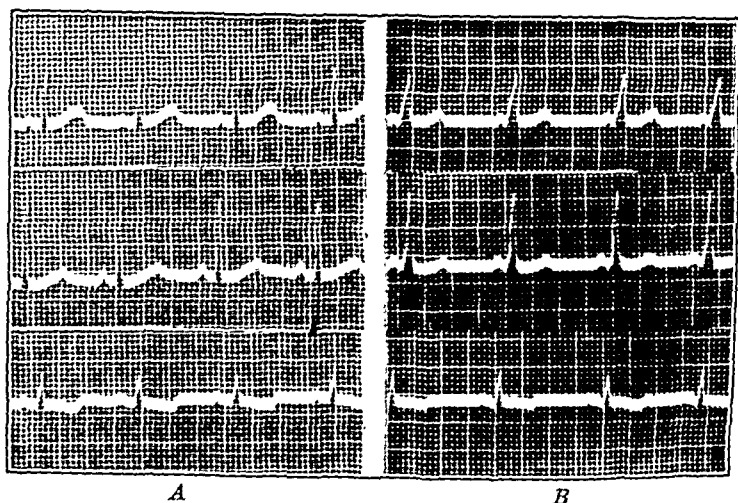


FIG. 1.—A, The only normal tracing obtained in the course of observation. The QRS duration is about 0.04 sec. The tracing is apparently the result of quinidine. B, The abnormal tracing. Note that the duration of the QRS complex is about 0.08 sec.

**Case Report.** A 52 year old painter was admitted with the chief complaint of pain in the left hip region. He also had occasional mild discomfort in the precordium, not accentuated by effort. A diagnosis of monostotic Paget's disease of the left ilium was made. An ECG taken on admission revealed a short P-R interval and a QRS complex of about 0.08 sec. (Fig. 1B). It was thought at the moment that the tracing represented a nodal rhythm. Another glance at the ECG however, revealed the presence of a slur on the upstroke of  $R_1$  and  $R_2$ . It then occurred to us that the ECG may possibly represent a *modified* Wolff-Parkinson-White syndrome.

The patient was followed for a period of 1 year. About 75 tracings were secured and all of them, with the exception of those which were the result of special studies, presented the same structural characteristics: a short P-R interval and an abnormal QRS complex of normal duration.

Special investigations were instituted in accord with the methods previously

employed.<sup>2,3</sup> The drugs used in an attempt to influence the electrocardiographic pattern were as follows: quinidine sulfate, digitalis, prostigmine methylsulfate and atropine sulfate.

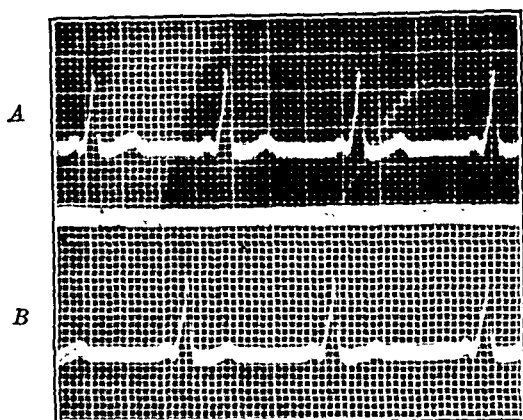


FIG. 2.—The effect of digitalis on the duration of the QRS complex. *A*, Lead I of a tracing secured immediately before the administration of Digitalin-Nativelle. *B*, Lead I of a tracing obtained 6 hours after oral administration of 1.2 mg. of Digitalin-Nativelle. Note a definite widening of the QRS complex.

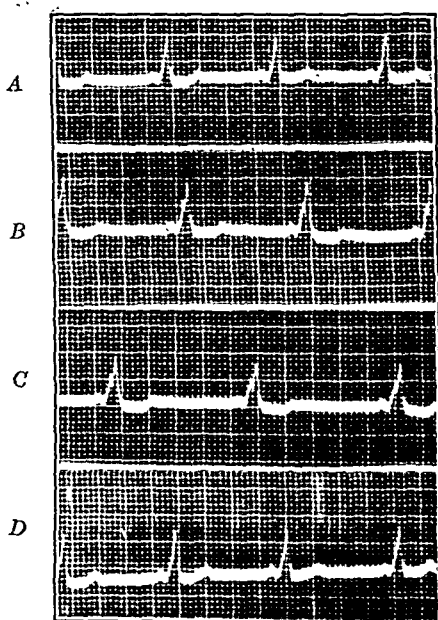


FIG. 3.—The effect of digitalis and prostigmine on the duration of the QRS complex. *A*, Lead I of a tracing obtained after 7 cat units of digitalis leaf were given over a period of 3 days. *B*, Lead I of a tracing obtained 3 days later in the course of which 8 additional cat units of digitalis leaf were given. Note definite widening of the QRS complex. *C*, Lead I of a tracing secured 20 minutes after intramuscular administration of 2 cc. of a 1:2000 solution of prostigmine methylsulfate. The drug was given immediately after tracing *B* was obtained. Note width (and form) of the QRS complex. *D*, Lead I of a tracing taken 21 days later. Note that duration of the QRS complex is that of the predominant type. Shortening of the QRS complex is apparently due to the elimination of digitalis.

Quinidine in various doses was administered orally on 4 occasions. On 1 occasion 10 gr. of the drug was given at 7 A.M. and a similar dose at 10 A.M.



At 11 A.M. a normal sinusal tracing was obtained (Fig. 1A). This was the only normal ECG obtained in the course of observation.

Digitalis was administered 6 times. The result was *conspicuous* widening of the QRS complex (Fig. 2B and 3B).

Prostigmine was given intramuscularly on 3 occasions. The result was a widening of the QRS complex (Fig. 3C and 4B).

Atropine was administered intravenously once, shortly after the administration of prostigmine. The result was a nodal rhythm(?) (Fig. 4C).

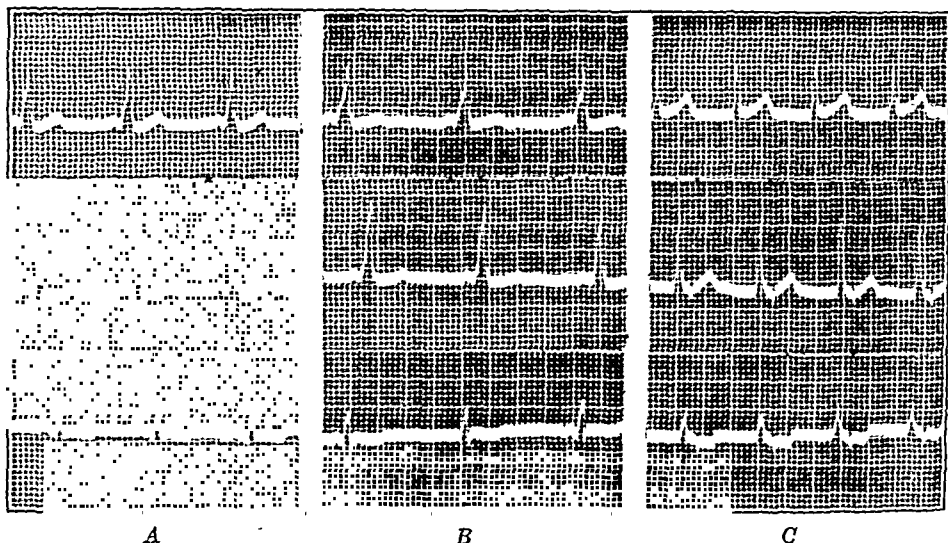


FIG. 4.—The effect of prostigmine and atropine on the form of the QRS complex. A, Control tracing obtained immediately before the administration of prostigmine. B, Tracing obtained 20 minutes after the intramuscular administration of 2 cc. of prostigmine methylsulfate, 1:2000 solution. C, Tracing secured immediately after the intravenous administration of atropine sulfate,  $\frac{1}{5}$  gr. The drug was given immediately after tracing B was developed. Note change in rhythm. The QRS complexes are of the supraventricular type and resemble the normal sinusal picture in Figure 1A.

**Comment.** The effect of cholinergic drugs (including digitalis), atropine sulfate and quinidine sulfate on the syndrome of short P-R interval and prolonged QRS complex was discussed in detail in 2 previous papers.<sup>2,3</sup> The purpose of this report is to show that prolongation of the QRS complex is not an essential criterion of the Wolff-Parkinson-White syndrome. The classical picture of the syndrome was reproduced in our case by making more "vagus substance" (acetylcholine) available. In other words, the difference between the case presented here and the classical picture of the Wolff-Parkinson-White syndrome is quantitative rather than fundamental in nature. The duration of the QRS complex is apparently, as stated elsewhere,<sup>2,3</sup> an expression of the degree of A-V node depression, caused by available "vagus substance."

The ECG pattern in our case could be looked upon as the resultant of the sinusal impulse traveling down to the ventricles through 2 pathways simultaneously: the normal A-V conduction system, and an aberrant atrio-ventricular conduction mechanism. Depression of the A-V node by cholinergic drugs causes the sinusal impulse to travel through the aberrant pathway exclusively; earlier arrival of the stimu-

lus to one of the ventricles registers a short P-R interval, but the asynchronous excitation of the two ventricles produces a prolongation of the QRS complex in the ECG. Quinidine, on the other hand, has a greater affinity for the aberrant conduction tissue, depressing it and thus causing the impulse to travel through the A-V node exclusively, describing in the ECG a normal sinusal pattern.

The prerequisite for the Wolff-Parkinson-White syndrome is the presence in the human heart of a congenital anomaly, an aberrant atrio-ventricular pathway. This may be the reason why the majority of the cases reported are in the younger age group. Our patient never had an ECG tracing done prior to his admission to the hospital. But even the assumption that his ECG was previously normal does not exclude the possibility of a dormant aberrant pathway. It is conceivable that a circulatory difficulty of the A-V node due to coronary sclerosis may sufficiently depress its functional activity to permit the aberrant mechanism to take over some of the conduction function.

The explanation of the *nodal rhythm* (?) in Figure 4C is not simple. "If the auriculo-ventricular node is partially released from the influence of the vagus nerve, while the sinus node is still relatively under the control of this nerve, a nodal rhythm may appear spontaneously." This is the explanation given by Wilson in his paper on "The Production of Atrio-ventricular Rhythm in Man After the Administration of Atropine."<sup>5</sup> Another possible explanation in this case is as follows: Atropine relieves the A-V node from the influence of the vagus nerve. Conduction through the A-V node is accelerated so much as not to register a P-R segment. The P wave following the QRS complex is an expression of retrograde conduction through the aberrant A-V pathway.

**Summary and Conclusion.** A case is presented with a short P-R interval and an abnormal but *not prolonged* QRS complex. Prolongation of the QRS complex was achieved through the influence of cholinergic drugs. In this manner the syndrome of short P-R interval and prolonged QRS complex was reproduced. It would therefore appear that the width of the QRS complex in this syndrome is merely an expression of the quantity of "vagus substance" available, and that the actual criteria of the Wolff-Parkinson-White syndrome are: a short P-R interval and an abnormal but not necessarily prolonged QRS complex.

In view of this, and of the available histologic evidence of the existence of an aberrant A-V conduction pathway, it is suggested that the syndrome be known as the "*aberrant atrio-ventricular conduction*."

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## THE SIGNIFICANCE OF THE PULMONARY DIASTOLIC MURMUR IN CASES OF MITRAL STENOSIS

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THE origin of the soft-blowing diastolic murmur heard over the pulmonic area in patients with mitral stenosis has aroused considerable interest since the time of Graham Steell and Pawinski. No unity of view has been reached, although most authors consider the murmur as purely functional.

Graham Steell<sup>23</sup> in 1888 described "a murmur due to pulmonary regurgitation, such regurgitation occurring independently of disease or deformity of the valvès, as the result of long-continued excess of blood pressure in the pulmonary artery." He defined it as a functional murmur very variable in intensity, now distinctly heard, at other times "indistinct or inaudible." A few years later Pawinski<sup>16</sup> described the same auscultatory phenomenon in patients with mitral stenosis and found at postmortem the signs of long-standing hypertension in the pulmonary artery. Since that time the soft diastolic murmur has been recognized as one of the occasional findings in mitral stenosis, and has been accepted as a functional murmur associated with extreme dilatation of the pulmonary artery and present during episodes of heart failure. It is, however, rarely heard. Cases have been reported by Vaquez and Magniel,<sup>26</sup> Ribierre,<sup>18</sup> Laubry and Thomas,<sup>7</sup> Scimone,<sup>22</sup> White,<sup>27</sup> Scherf,<sup>20</sup> Harvier and co-workers,<sup>5</sup> Schwartz,<sup>21</sup> and others. Postmortem findings, when available (as in 6 cases of Scherf<sup>20</sup> and 1 of White<sup>27</sup>), revealed dilatation of the pulmonary artery and undamaged pulmonic valves. Sussman and co-workers<sup>24</sup> described what they called a Graham Steell murmur in cases of Lutembacher's syndrome.

**Case Reports.** CASE 1. *Mitral stenosis, pulmonic insufficiency.* John McS., a 23 year old white male, was first seen in May, 1942. One brother died of rheumatic heart disease and pneumonia. The patient had recurring episodes of joint pains during the previous 10 years, once accompanied by slight fever and lassitude, and during this period he occasionally raised blood-streaked sputum. Recently he had dyspnea and precordial distress, at times severe precordial pain radiating to the left arm.

*Physical examination* showed a tall, slender young man with severe cyanosis especially pronounced around the lips and the nose-tip, but no clubbing of the fingers or toes. The pulse was weak, small and completely irregular. The chest was deformed due to protrusion of the sternum and precordial area. Multiple pulsations were visible in many intercostal spaces and the epigastrium, particularly in the apical region. Palpation revealed a diastolic thrill over the apex and the mid-precordium, and by percussion, a rounded cardiac profile was outlined. Auscultation revealed the following signs: (1) A rumbling diastolic murmur (Grade 5) extending over an area from the 4th rib to the apex. (2) A soft blowing diastolic murmur (Grade 3) confined largely to the pulmonic valve area. (3) A short harsh systolic murmur over the xyphoid

process (Grade 2). (4) A more prolonged harsh systolic murmur (Grade 3) over the pulmonic area. (5) The second pulmonic sound was loud and snapping.

There were no peripheral signs of aortic insufficiency and the blood pressure was 140/90. There were no signs of congestive failure. The electrocardiogram showed auricular fibrillation and marked right axis deviation.

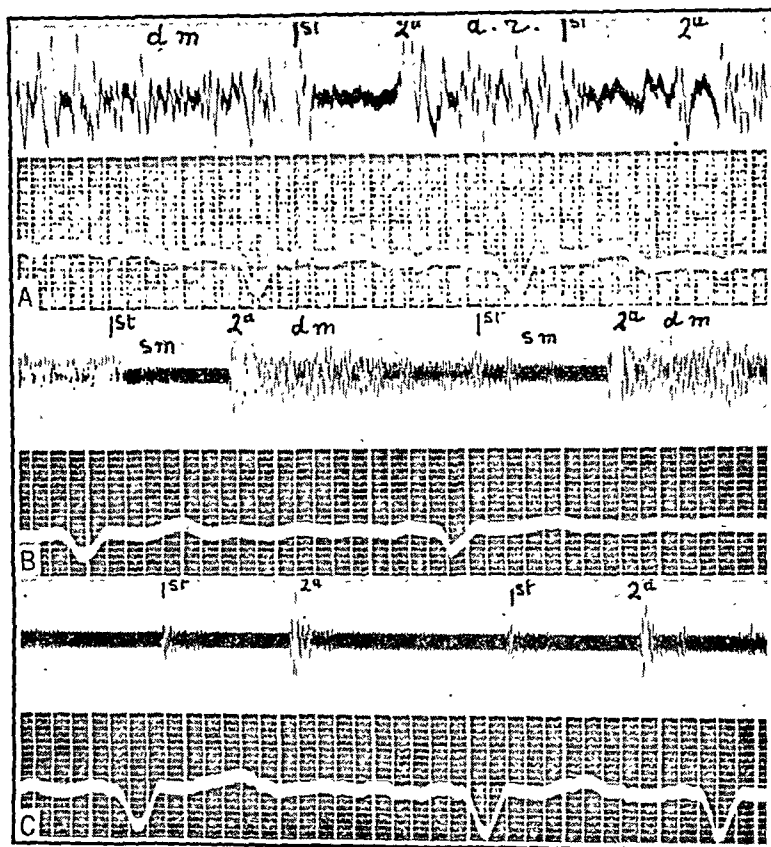


FIG. 1.—Case 1. A, Phonocardiogram recorded at the apex with stethoscopic microphone; electrocardiogram. B, Phonocardiogram recorded at the pulmonic area with logarithmic microphone; electrocardiogram. C, Phonocardiogram recorded at the aortic area with logarithmic microphone; electrocardiogram.

There was slight secondary anemia, with normal white cell count and differential. The blood Wassermann and Hinton tests were negative. The urine was normal and had a specific gravity of 1.026. Oxygen saturation of the femoral arterial blood was 90%. Arm to tongue circulation time (decholin) was 44 seconds, and the arm to lung circulation time (ether) was 11 seconds. Roentgen ray examination disclosed a markedly enlarged heart, striking prominence of the pulmonary artery, a narrow aorta, dilatation of the left and right auricles and prominence and pulsation of the hilar vessels.

Phonocardiograms confirmed the auscultatory findings (Fig. 1). Of particular interest were the records obtained over the pulmonic and aortic areas showing a high-pitched diastolic pulmonic murmur with very slight transmission to the aortic valve area.

The pulmonic diastolic murmur was present at all examinations during a 2-year period of observation and showed a tendency to increase in intensity with the appearance of a diastolic thrill.

**CASE 2.** *Mitral stenosis, interauricular septal defect, pulmonic insufficiency.* Mary McD., a 49 year old white housewife was first seen in March, 1940, complaining of dizziness, palpitation and dyspepsia. At the age of 4 she had pertussis, at which time a diagnosis of heart disease was made. At the ages of 11 and 14 she had rheumatic fever, and 10 years later a mitral lesion was recognized for the first time. Shortness of breath was noted since the age of 11. Four years prior to examination she began to have nocturnal attacks of squeezing precordial pain. During the past 10 years dizziness, palpitation, intense sweating, swelling of the ankles and cough with bloody sputum occurred occasionally. More recently a severe attack of dizziness was followed by numbness of the right half of the body. She married at the age of 21 and had 15 pregnancies. Twelve of these were interrupted by abortion, 3 ended normally. The 3 children are in good health.

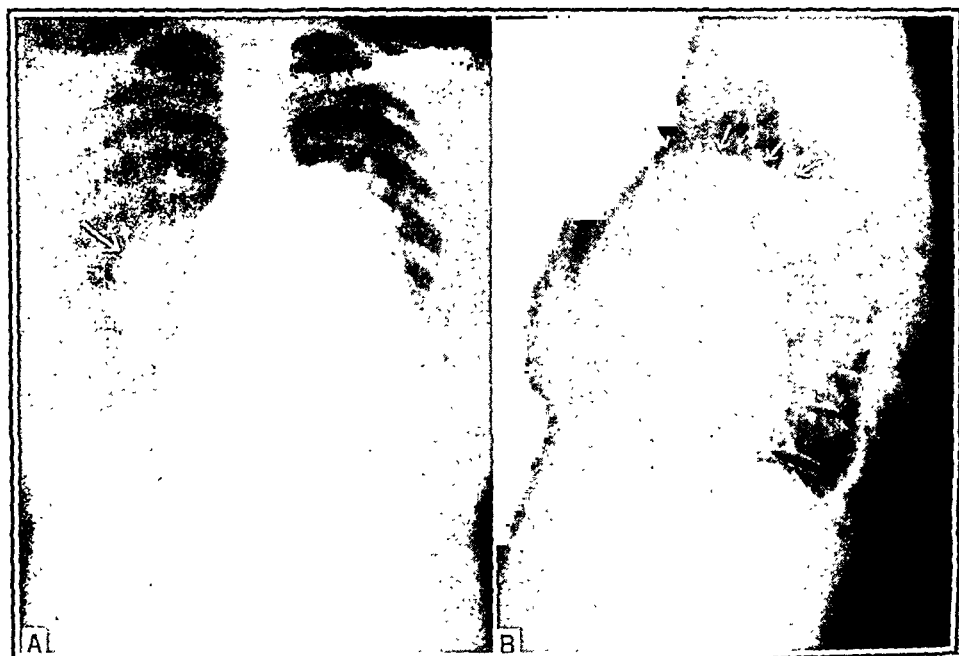


FIG. 2.—Case 2. Roentgen ray of the chest. A, Frontal view. The shadow in the right mid-lung field is a dilated branch of the pulmonary artery. B, Left anterior oblique, showing the dilated pulmonary artery and left branch.

*Physical examination* showed a strongly built woman, moderate cyanosis of the lips, without clubbing of the fingers or toes. The pulse was small and regular at a rate of 100. The right radial pulse seemed at times smaller than the left. There was intense pulsation of the external jugular veins and of the carotid arteries. A diastolic thrill was palpable over the apex. Percussion revealed marked cardiac enlargement. Auscultation disclosed a rumbling diastolic murmur at the apex and blowing systolic and diastolic murmurs in the second and third left interspaces. The latter murmurs were fairly well transmitted toward the left clavicle, but very poorly toward the right side and toward the suprasternal notch, and were inaudible over the carotids. The blood pressure was 134/84 and there were no peripheral signs of aortic insufficiency.

Laboratory studies showed normal blood cell counts and urine, and the blood Hinton and Wassermann tests were negative. Electrocardiogram showed normal sino-auricular rhythm, right axis deviation, and inverted or diphasic T waves in Leads I and II. Phonocardiograms confirmed the aus-

cultatory signs (Fig. 3). The arm to tongue circulation time (decholin) was 25 seconds. Roentgen ray examination revealed moderate enlargement of the right ventricle, but only slight dilatation of the left auricle, and a narrow aorta. The pulmonary conus was markedly prominent, measuring 5.6 cm. in diameter, and the pulmonary artery branches were markedly dilated on both sides; the hilar shadows on the right showed expansile pulsation (Fig. 2). There was no evidence of chronic pulmonary congestion.

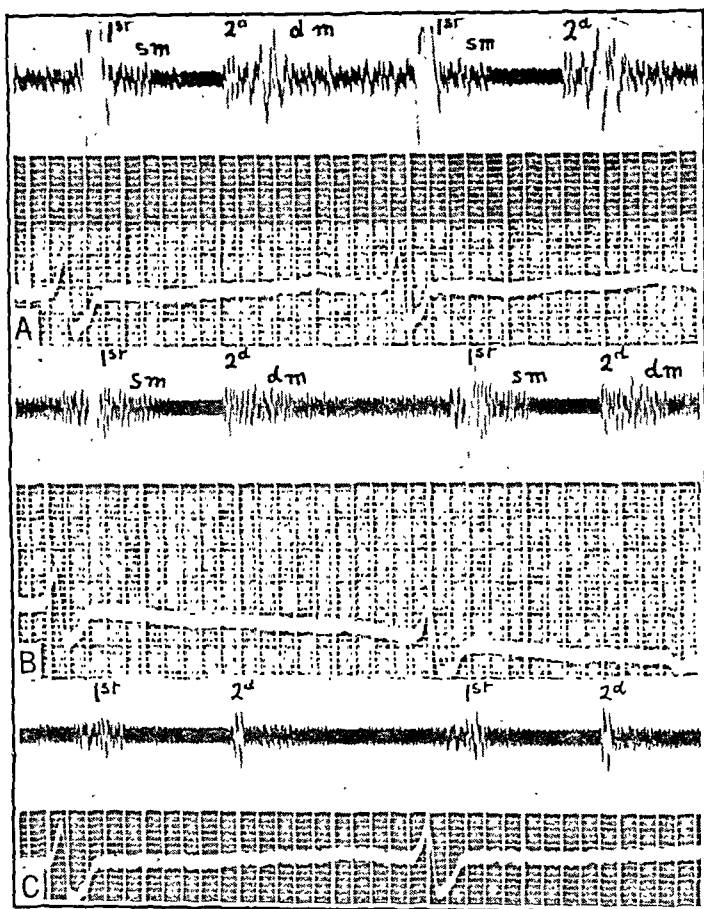


FIG. 3.—Case 2. A, Phonocardiogram recorded at the apex with stethoscopic microphone; electrocardiogram. B, Phonocardiogram recorded at the pulmonic area with logarithmic microphone; electrocardiogram. C, Phonocardiogram recorded at the aortic area.

She was digitalized and thereafter edema of the ankles or other signs of congestive failure were absent. The cardiovascular signs remained unchanged at 15 subsequent examinations.

**CASE 3.** *Mitral stenosis, interauricular septal defect pulmonic insufficiency.* H. S., a 21 year old white male, was first seen in the Out-Patient Department of the Beth Israel Hospital in 1937. After an attack of scarlet fever 10 years previously, he was told that he had heart disease. Shortness of breath and precordial pain occurred with increasing severity in recent months. There was no history of rheumatic fever or joint pains.

*Physical examination* showed faint cyanosis of the lips, but no clubbing of the fingers or toes. The apex beat was visible in the 5th interspace, 11 cm. from the midsternal line and was diffuse. The right border of the heart was

3.5 cm. from the midsternal line. Systolic and diastolic thrills were palpable over the apex. A rough-blowing systolic murmur and a rough diastolic rumble were heard at the apex and a soft-blowing diastolic murmur in the 2nd left interspace. The latter was always present and increased in intensity during the following 11 years. No peripheral signs of aortic insufficiency were present. The pulse was 98, the blood pressure 120/70.

The blood counts, urine examination and blood Kahn and Hinton reactions were normal. Electrocardiogram showed a normal sinus rhythm, marked right axis deviation, diphasic  $T_2$  and inverted  $T_3$ .  $P_1$  was notched,  $P_3$  was prominent. Roentgen ray examination showed enlargement of the right and left ventricles, a small aorta, aneurysmal dilatation of the pulmonary artery, but no dilatation of the left auricle.

Phonocardiograms confirmed the auscultatory findings (Fig. 4).

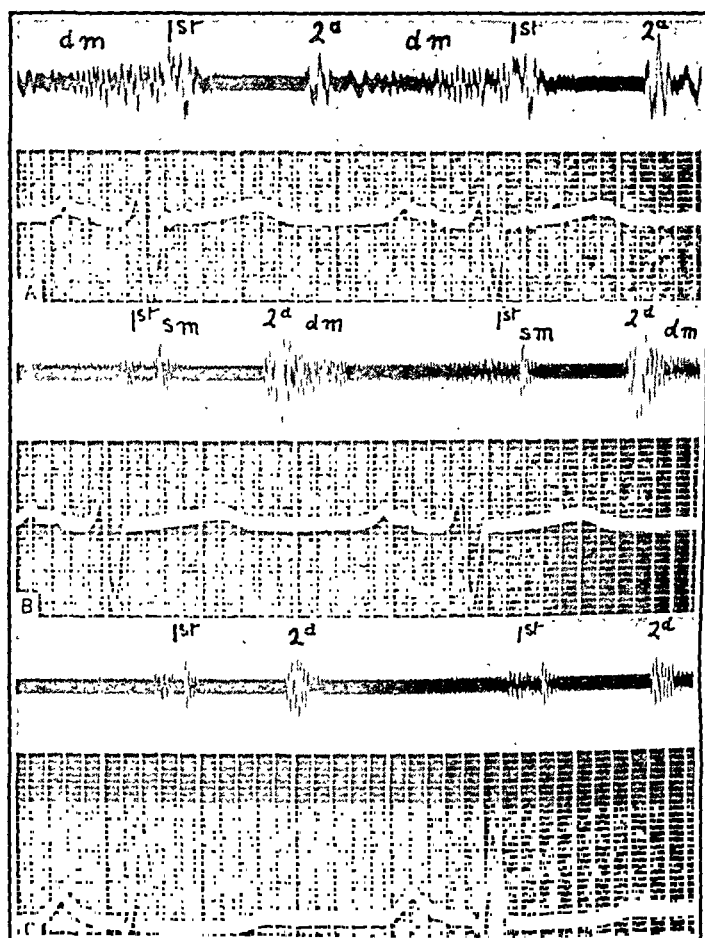


FIG. 4.—Case 3. A, Phonocardiogram recorded at the apex with stethoscopic microphone; electrocardiogram. B, Phonocardiogram recorded at the pulmonic area with logarithmic microphone; electrocardiogram. C, Phonocardiogram recorded at the aortic area; electrocardiogram.

**Discussion.** To facilitate the differential diagnosis between aortic and pulmonic insufficiency, a table was constructed (Table 1) from the writings of several authors (Pezzi,<sup>16,17</sup> Schwartz,<sup>21</sup> Harvier *et al.*,<sup>5</sup> White,<sup>27,28</sup> Sussman *et al.*<sup>24</sup>). Applying these criteria to the cases here

reported we made a diagnosis of pulmonic insufficiency in each one. The signs remained essentially unchanged on repeated observations over a period of years. Two possibilities were considered as explanation for the pulmonic insufficiency:

(a) *Functional insufficiency of the pulmonary valve* (Graham Steell murmur) due to temporary dilatation of the pulmonary conus or artery associated with congestive failure.

TABLE 1.—MITRAL STENOSIS WITH AORTIC AND WITH PULMONARY INSUFFICIENCY

Sign	Mitral stenosis plus aortic insufficiency	Mitral stenosis plus pulmonary insufficiency
Cyanosis	Moderate	More intense
Axis deviation	Slight right axis deviation or no deviation	Marked right axis deviation
Pulse pressure	Ample	Small
Diastolic pressure	Low	Normal or high
Strong systolic pulsation (inspection, palpation, graphic tracing) with possible systolic thrill	Present over suprasternal notch and lateral cervical regions	Present over second left interspace
Systolic murmur (auscultation, phonocardiography)	Present over second right interspace, transmitted to suprasternal notch and to carotid arteries	Present over second left interspace transmitted toward left clavicle
Diastolic murmur	Radiating along left sternal border	Restricted to a small area
Size of pulmonary artery and of aorta (Roentgen ray)	Pulmonary artery either slightly dilated or normal; aorta either normal or dilated	Very marked dilation of pulmonary artery (resembling aspect of some congenital hearts); small aorta
Pulsations of pulmonary artery and of aortic arch (Roentgen ray; Roentgen-kymography)	Increased pulsation of aortic arch; normal pulsation of pulmonary arch	Small pulsation of aortic arch, very ample pulsation of pulmonary arch and of pulmonary branches
Hilus dance (fluoroscopy; Roentgen-kymography)	Absent	Present

(b) *Organic pulmonic insufficiency* due to inflammatory lesions of the valves or permanent dilatation of the pulmonary conus or artery.

The inconstancy of the murmur and its more common occurrence during congestive failure were emphasized by Graham Steell<sup>23</sup> and regarded as evidence of its functional origin. White<sup>27</sup> was of the same opinion. In Scherf's<sup>20</sup> cases the murmur was found only late in life and during congestive failure. Since in our cases the murmur was constantly present and independent of failure, a functional origin of the pulmonic insufficiency was considered an inadequate explanation.

*Stretching of the pulmonary artery secondary to arteriosclerosis* was regarded as the cause of pulmonic insufficiency by Laubry and Thomas,<sup>7</sup> Harvier *et al.*,<sup>5</sup> Scimone,<sup>22</sup> and others. In pulmonary arteriosclerosis unaccompanied by mitral stenosis, a pulmonic diastolic murmur occurs only in some of those cases in which there is also an *aneurysm of the pulmonary artery* (Arrillaga<sup>2</sup>). In interauricular septal defect with or without an associated mitral stenosis, marked dilatation of the pulmonary artery is usually present, but a pulmonic diastolic murmur occurs in only some of the cases (Abbott,<sup>1</sup> Lutembacher<sup>10,11,12</sup> Roesler,<sup>19</sup> Laubry and Thomas<sup>7</sup>). Even in cases of *aneurysm of the pulmonary artery due to syphilitic arteritis*, the murmur may be absent. In 2 cases observed by one of us (Luisada,<sup>8,9</sup>) one had no diastolic murmur, the



other only a very faint one. The conclusion follows that increased pulmonary pressure and arteriosclerosis and dilatation of the pulmonary artery do not always give rise to pulmonic insufficiency. An analogous situation exists in cases of arterial hypertension and arteriosclerosis of the aorta.

The studies of Gouley and Eiman,<sup>4</sup> von Glahn and Pappenheimer,<sup>3</sup> and Kugel and Epstein<sup>6</sup> indicate that lesions of the pulmonary artery and pulmonary valve may occur in rheumatic fever. Kugel and Epstein found rheumatic involvement of these structures in 17 out of 24 cases, 2 with gross changes in the pulmonary artery and 6 with verrucæ on the pulmonic valve. Microscopic study showed that 14 out of 24 cases had evidence of pulmonary valvulitis and in 3 of these Aschoff bodies were present. The most constant site of the arterial lesions was the insertion of the valves at the root of the pulmonary artery. These facts offer evidence to support the contention that the constant pulmonic insufficiency observed in our cases depends on deformity of the valves or permanent dilatation of the vascular structures, or both, and not on transient functional alterations secondary to congestive failure or fluctuations in pulmonary artery pressure.

**Summary.** 1. Three cases of mitral stenosis, 2 with associated interauricular septal defect, are described in which pulmonic insufficiency was constantly present and independent of congestive failure. None have died. Phonocardiographic records of the murmurs are included.

2. The clinical signs of pulmonary insufficiency and its differentiation from aortic insufficiency are reviewed from the literature and tabulated.

3. Pulmonary insufficiency is not always transient and functional in cases of mitral stenosis with or without interauricular septal defect, but may be permanent and organic as in the cases here reported. The nature of the possible organic changes is discussed.

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## SPONTANEOUS MEDIASTINAL EMPHYSEMA WITH PNEUMOTHORAX SIMULATING ORGANIC HEART DISEASE

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In a paper dealing with the differential diagnosis of coronary occlusion, Hamman<sup>3a</sup> discussed 3 cases of interstitial emphysema of the lungs in which the pain was similar in type and distribution to that seen in coronary artery disease. In this and later publications<sup>3b,c</sup> he called attention of the medical profession to the clinical picture resulting from the spontaneous occurrence of mediastinal emphysema. In 1937, Scott<sup>8</sup> reported 2 cases of the syndrome and again called attention to the fact that the pain of mediastinal emphysema may simulate and must be differentiated from that of angina pectoris. Since then other investigators have mentioned the necessity of considering spontaneous mediastinal emphysema in the differential diagnosis of pain in the chest.

In spite of the increasing number of case reports of spontaneous mediastinal emphysema in the literature, they are still scarce enough to lead one to believe that the condition is rare. In the past 3 years the author has seen 8 cases of the syndrome in soldiers. In 6 of these a left-sided pneumothorax was demonstrated roentgenologically. It is the purpose of this paper to record the findings in 4 of these cases and to point out the similarity of the condition to organic heart disease.

**Case Studies.** CASE 1. A white male, aged 38, was admitted to the Station Hospital on November 25, 1943, complaining of pain in the left chest. He dated the onset of his present illness to November 20, 1943, when he was awakened from sleep by a sudden, severe pain in the left parasternal region at the level of the third rib. This pain spread rapidly over the left chest anteriorly and extended to the interscapular region posteriorly. Associated with this pain he rapidly became short of breath. His respiratory distress was much ameliorated when he sat up. The pain gradually subsided so that by morning it had been replaced by a dull ache. In spite of this pain and moderate exertional dyspnea, the patient was able to do full duty until November 26, when he developed a pleuritic type of pain in the left axillary region. He gave a history of a dry, non-productive cough of 2 weeks' duration. In January and September, 1943 he had experienced 2 similar attacks of pain in the left chest which came on suddenly, did not radiate and were not associated with dyspnea. The first attacks lasted a week and the second, 3 days. The pain

was not as severe as that experienced during the present illness. The patient was examined at sick call both times but Roentgen rays were not taken.

*Physical examination* revealed a well-developed, adult male in no acute distress. There were no abnormalities of the head, eyes, ears, nose or throat. The trachea was not displaced. Respiratory excursions were markedly diminished on the left side of the chest. Tactile fremitus was diminished and the percussion note was hyperresonant over the entire left chest with extension of the hyperresonant sound to the full capacity of the pleural space. The breath sounds and voice sounds were absent over this side. The right border of cardiac dullness was percussed 6 cm. to the right of the midsternal line in the fourth interspace. The sounds were muffled, the rate was 68 per minute and the rhythm was regular. No murmurs were heard. Over the lower two-thirds of the sternum, there were audible high-pitched, crunching, crackling sounds during both systole and diastole. These sounds became louder in the upright position, especially in full inspiration. The arterial pressure was 106 mm. Hg systolic and 64 diastolic. There was no evidence of emphysema in the subcutaneous tissues of the neck or chest wall. The abdomen was soft and no organs or masses were felt.

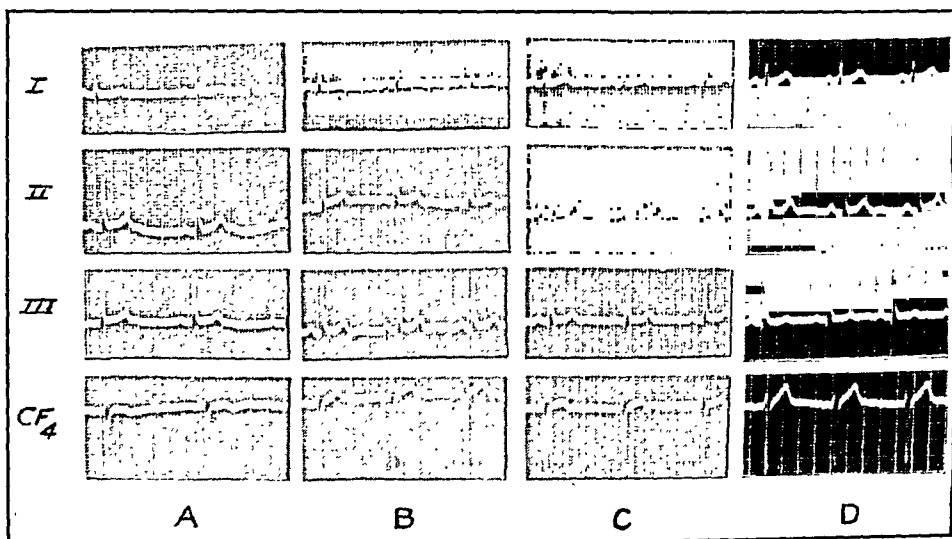


FIG. 1.—Case 1. Serial electrocardiograms.

The patient's course in the hospital was afebrile and asymptomatic. Hamman's sign gradually decreased in intensity and finally disappeared on December 14, 1943.

*Laboratory Data.* Urine: acid, clear, specific gravity 1.014, no albumin or sugar, and an occasional epithelial cell and W.B.C. per high-power field. Blood: erythrocytes 3,900,000 per c.mm.; hemoglobin, 85% (Newcomer); leukocytes, 5400 with 61% neutrophils and 39% lymphocytes. The blood sedimentation rate (Westergren) was 17 mm. after 60 minutes.

Radiographic examination of the chest on November 24, 1943 revealed a 40% collapse of the left lung. There was an almost total collapse of the left upper lobe and a partial collapse of the left lower lobe. The mediastinal structures were shifted moderately to the right side. In the antero-posterior, oblique and lateral views no pneumomediastinum could be demonstrated. Examination on December 4 and December 12, 1943 revealed rapid reëxpansion of the left lung.

*Electrocardiograms.* The first electrocardiogram (Fig. 1A), taken on the day of admission, revealed a sinus mechanism with an occasional auricular

extrasystole, a rate of 54 per minute, and a conduction time of 0.16 sec. Lead I shows a flat T wave less than 1 mm. in height. In Leads II and III, the S-T segments were slightly elevated. In the precordial lead, the initial upward deflection measured 0.5 mm. and the T wave was inverted.

An ECG (Fig. 1B) taken November 27, still revealed a flat T wave in Lead I and elevation of the S-T segments in Leads II and III. In the precordial lead, the initial upward deflection measured 2 mm. On December 7 (Fig. 1C) the T wave in Lead I was normal. The patient's normal ECG on December 15 (Fig. 1D) revealed a sinus mechanism, a rate of 66 per minute, and conduction time of 0.16 sec. The T waves were upright and normal in all leads and the initial upward deflection in the precordial lead measured 3 mm.



FIG. 2.—Case 2. Oblique roentgenogram illustrating air in the posterior mediastinum.

CASE 2. A white male, aged 23, was admitted to the station hospital on November 29, 1943, complaining of pain in the left chest. On the morning of admission, while doing calisthenics, he developed a sudden, sharp, knife-like pain under the left scapula. The pain extended over the left supraclavicular region to the anterior chest wall. Associated with this pain he became very dyspneic and was unable to take a deep breath. The pain and dyspnea persisted up to the time of admission to the hospital. He stated that he had a slight non-productive cough for the past few weeks and a head cold for the past 3 days.

*Physical examination* revealed a well developed young adult, moderately dyspneic but in no acute distress. The pharynx appeared granular and injected. The trachea was deviated to the right side of the midline. Respiratory excursions were decreased on the left side. The percussion note was hyperresonant, tactile fremitus, breath sounds, and vocal fremitus were diminished and no râles were heard on the involved side. The area of cardiac dullness was not elicited. The rhythm was regular, rate 72 per minute and no murmurs were heard. The arterial pressure was 130 mm. Hg systolic and 88 diastolic.

The patient was not seen again by the author until December 4, at which time the area of cardiac dullness was replaced by a hyperresonant percussion note and loud, crackling, crunching sounds in both systole and diastole were heard over the whole sternum. These sounds were much louder in full expiration.

The patient's course in the hospital was afebrile. He complained occasionally of mild substernal pains. Hamman's sign persisted until December 16. It varied in intensity and character. At times it had a clicking quality and at other times it was loud, crunching or popping. It was loudest in full expiration with the patient in the upright position and audible posteriorly between the spine and left scapula. The patient frequently heard the noise in his chest and described it as a "grinding sound."



FIG. 3.—Case 2. Arrow points to air along the mediastinopleural reflexion of the left lung.

*Laboratory Data.* Urine: acid, clear, specific gravity 1.020, no albumin, sugar, cells or casts were found. Blood: erythrocytes 5,650,000 per c.mm.; hemoglobin 95% (Newcomer); leukocytes 5850 with 74% neutrophils, 24% lymphocytes and 2% eosinophils. The blood sedimentation rate (Westergren) was 7 mm. after 60 minutes.

Radiographic examination of the chest on November 29, 1943 revealed a pneumothorax in the left pleural cavity with approximately 50% collapse of the left upper lobe and 25% collapse of the left lower lobe. There was evidence of moderate dextro-rotatory scoliosis in the thoracic region with the apex of the curve at the level of the 7th dorsal vertebra. The anteroposterior, lateral and oblique views failed to reveal air in the mediastinal tissues. On December 6 (Fig. 2), radiographic examination revealed the presence of air in the posterior mediastinum. On December 9, a small amount of air was demonstrated in the mediastinal region along the upper portion of the left cardiac

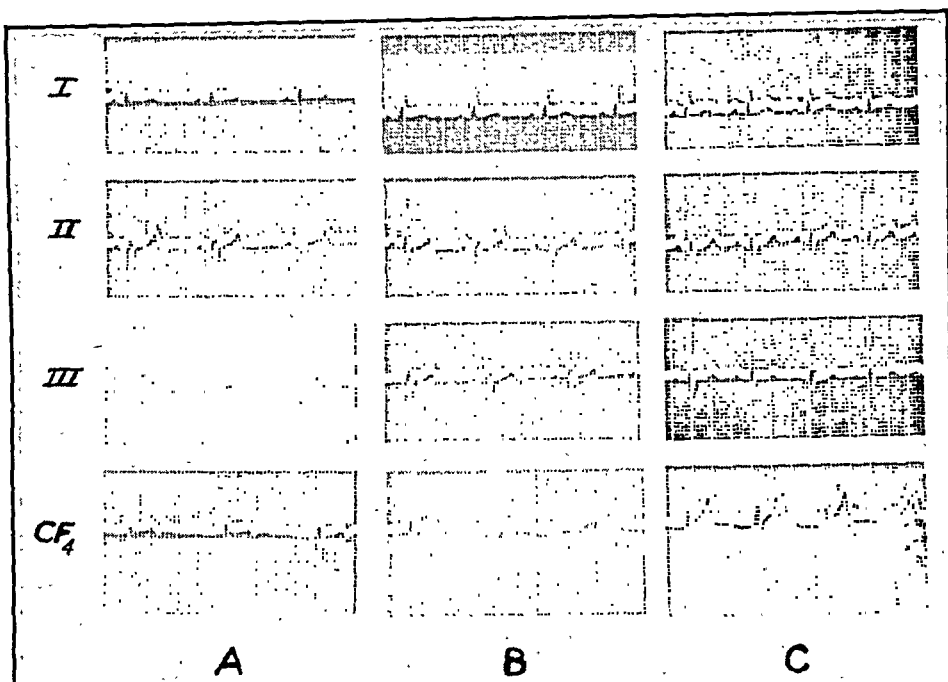


FIG. 4.—Case 2. Serial electrocardiograms.

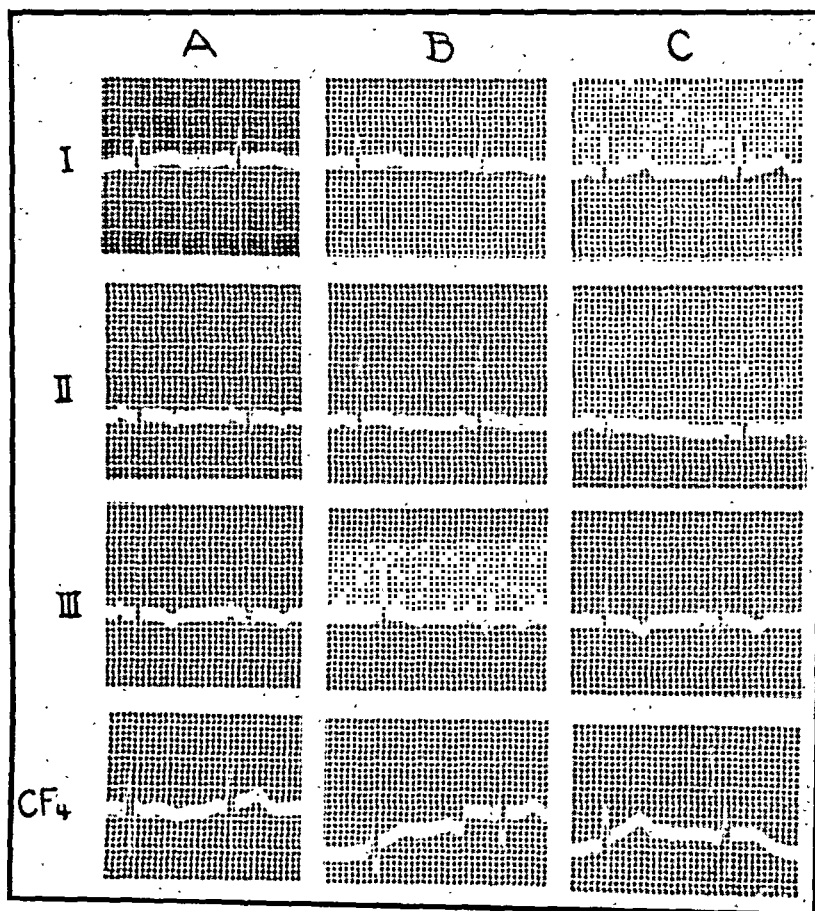


FIG. 5.—Case 3. Serial electrocardiograms.

contour and a small collection of air was noted along the mediastinopleural reflection of the left lung (Fig. 3).

*Electrocardiograms.* The first tracing (Fig. 4), taken on December 4, revealed a sinus mechanism, a rate of 66 per minute and a conduction time of 0.14 sec. The QRS complexes were slightly slurred and measured 0.08 sec. In the precordial lead, the initial upward deflection measured 0.5 mm. and the T wave was inverted. An ECG on December 10 (Fig. 4B) revealed no significant change, except in the precordial lead where the initial upward deflection measured 1 mm. and the T wave was upright. The patient's normal ECG on December 15 (Fig. 4C) revealed a sinus mechanism, a rate of 100 per minute and a conduction time of 0.14 sec. The T waves were upright and normal in all leads and the initial upward deflection in the precordial lead measured 3 mm.

CASE 3. A white soldier, aged 23, was admitted to the hospital on January 20, 1942, complaining of precordial pain and numbness of the left arm. On December 15, 1941 while instructing soldiers on the use of the mortar, the patient experienced a sudden sharp, knife-like pain in the precordial region associated with marked shortness of breath. The pain was increased by any attempt to take a full breath. He was admitted to a local station hospital shortly afterward. About 1 hour after the onset of precordial pain, while lying quietly in bed, he developed numbness and tingling down the medial aspect of his left arm. This lasted about an hour and then disappeared. However, until shortly before he was discharged on December 22, 1941, he was conscious of a persistent, dull, aching pain in the precordial region. On December 20, his temperature rose to 101° F. and rapidly subsided. His course in the hospital was otherwise uneventful. He felt perfectly well until January 19, 1942, when he overexerted himself helping to extinguish a brush fire. While returning to camp, after a swim in the river, he suddenly developed the same type of precordial pain which he had experienced a month previously. The pain was sharp and knife-like, and associated with dyspnea and numbness and tingling of the left arm. The patient continued to work, and that night the pain became more severe and was accentuated by lying on the left side. The next morning he was sent to the hospital for an ECG. Because of inverted T waves in Leads II and III of the ECG, he was admitted for further study.

Physical examination revealed a well-developed, young adult male who did not appear acutely ill. The head, eyes, ears, and nose were normal. The tonsils were moderately enlarged and cryptic but no pus could be expressed from them. Respiratory excursions of the left side of the chest were limited and the breath sounds and voice sounds were diminished over the left chest anteriorly and posteriorly. The area of cardiac dullness was not enlarged, the rhythm was regular, the rate 80 per minute and no murmurs were heard. The arterial pressure was 110 mm. Hg systolic and 62 diastolic. Over the lower portion of the left chest anteriorly were audible low-pitched "clicking, crackling sounds" in systole and diastole, which became louder with each inspiration. The abdomen was soft and no organs or masses were felt.

Hamman's sign was still present on January 21 and then disappeared. The patient's course in the hospital was uneventful and asymptomatic. The temperature on the day of admission rose to 99.2° F. and thereafter was normal. He was discharged on February 7, 1942.

*Laboratory Data.* Urine: amber, clear, acid, specific gravity 1.030, no albumin, sugar, casts or cells. Blood: erythrocytes 4,400,000 per c.mm.; hemoglobin 80%; leukocytes 6600 with 67% neutrophils, 2% eosinophils and 31% lymphocytes. The Wassermann and Kahn blood tests were negative. One sputum examination revealed no tubercle bacilli. The tuberculin skin test was negative.

An ECG on January 20 (Fig. 5A) revealed a sinus mechanism with a rate of 84 per minute and an A-V conduction time of 0.14 sec. The T waves were flattened in Lead I and inverted in Leads II and III. On January 22 (Fig. 5B), the T waves were normal in Lead I, diphasic in Lead II, and inverted in Lead III. On January 30 (Fig. 5C), the T waves in Lead I were increased in amplitude; in Lead II they were diphasic, and in Lead III inverted.

Radiographic examination on January 20 revealed a slight compression of the left lung by pneumothorax. On January 27, the Roentgen ray revealed partial reëxpansion and, on February 2, complete reëxpansion of the lung.

CASE 4. A white soldier, aged 20, was admitted to the hospital on November 29, 1941 complaining of precordial pain. He dated the onset of his present illness to the afternoon of November 28, when he suddenly developed a sharp, stabbing pain in the left chest which radiated through to the back and up under the scapular region on the same side. He was slightly short of breath at the onset and could not take a deep breath. The severe pain persisted for about 1 hour and gradually subsided to a dull ache which was still present at the time of entry into the hospital. The admission diagnosis was "acute pericarditis." He gave no history of previous heart trouble, chest pain, dyspnea, cough, sputum, hemoptysis or weight loss.

*Physical examination* revealed a well developed, asthenic young male who did not appear acutely ill. The eyes, ears, nose, and throat were normal. There was no deviation of the trachea, and respiratory excursions were equal on both sides of the chest. The breath sounds and voice sounds were normally transmitted. The area of cardiac dullness was not enlarged, the heart sounds were normal, the rhythm regular, the rate 88 per minute, and no murmurs were heard. The arterial pressure was 130 mm. Hg systolic and 84 diastolic. The abdomen was soft and no organs or masses were felt.

On November 30, 1941 to-and-fro crepitations were heard to the left of the sternum over the apex of the heart. These were audible in systole and diastole during both phases of respiration, at times resembled a coarse pericardial friction rub and at other times were typical of Hamman's sign. These sounds were heard for three days and then disappeared. Except for a temperature of 99.2° F. on the day of admission, the patient's course in the hospital was afebrile. He was discharged January 17, 1942.

*Laboratory Data.* Urine: clear, acid, specific gravity 1.024 with no albumin, sugar, casts or cells. Blood: erythrocytes, 4,300,000 per c.mm.; hemoglobin, 75%; leukocytes, 7600 per c.mm. with 70% neutrophils, 13% eosinophils and 17% lymphocytes. A thick smear was negative for malarial parasites. The Wassermann and Kahn blood tests were negative. The blood sedimentation rate (Westergren) was 5, 3 and 3 mm. after 1 hour on 3 occasions. A stool examination was negative for ova and parasites. The tuberculin test was negative.

An ECG on November 29 revealed a sinus mechanism with a rate of 94 per minute and an A-V conduction time of 0.15 second. The QRS complexes measured 0.08 sec. and the T waves were upright and normal in all leads.

Radiographic examination on November 29 revealed a slight compression of the entire left lung by a pneumothorax with a small fluid level at the left base. The chest was otherwise clear. On December 9 the left lung was completely reëxpanded.

**Discussion.** The probable explanation of the genesis of spontaneous mediastinal emphysema is contained in the series of experiments by Macklin.<sup>4</sup> By overdistinging a lobe of the lungs of cats and other animals, he was able to demonstrate that air enters the perivascular sheaths of the pulmonary vessels presumably through ruptures in the walls of the alveoli. The bubbles of air coalesce as they dissect along these artificial tunnels toward the root of the lung and eventually break through into the mediastinum. These air bubbles may form large blebs that actually impede the pulmonary circulation. Occasionally the air may extend from the perivascular sheaths into the adjoining connective tissue and dissect a path toward the pleura where it forms a subpleural bleb. From the mediastinum the air tends to follow with predilection the fascial planes, particularly the sheaths



surrounding blood-vessels. It may spread upward into the neck, axilla or over the chest wall. It may extend forward between the parietal pleura and pericardium to appear as blebs overlying the heart or downward into the retroperitoneal space.

Clinically, the spontaneous type of mediastinal emphysema is characterized by the sudden, frequently alarming development of precordial or substernal pain. The severity of the pain depends largely on the degree of distention of the mediastinal tissues by air. It may radiate to the back, shoulder, neck or down the left arm as it does in angina pectoris. There is frequently an associated pressure sensation under the sternum. The duration of pain is variable, lasting from several hours to several days. Dyspnea, cyanosis, and orthopnea may occur but are not characteristic of the syndrome. From this brief discussion it is evident that the type of pain associated with spontaneous mediastinal emphysema may simulate that of coronary thrombosis, pericarditis, dissecting aneurysm, pulmonary embolism, and mediastinitis. The differential diagnosis depends entirely on the clinical examination.

In mediastinal emphysema, air may be detected in the subcutaneous tissues of the neck and anterior chest wall. The area of cardiac dullness may be replaced by a hyperresonant percussion note. The pathognomonic sign of mediastinal emphysema is the peculiar sound heard over the precordium on stethoscopy. It has been described as crunching, crackling, popping, crepitant, and so on; changes in position and phase of respiration may alter the intensity and quality of the sound. It is synchronous with the heart beat, and may be heard during systole, diastole or both phases of the cardiac cycle. Pneumothorax has been present in some of the reported cases. In uncomplicated cases, there is no evidence of serious constitutional disturbance. The temperature as a rule is normal with normal or slightly elevated pulse and respiration. The blood pressure, white blood count, and sedimentation rate are usually within normal limits. The electrocardiograms, in cases where they have been reported, have failed to reveal any significant changes. Roentgenographic demonstration of air in the mediastinum is diagnostic.

A study of the foregoing case histories leads to the appreciation of the difficulty one may encounter in distinguishing spontaneous mediastinal emphysema with an associated pneumothorax from organic heart disease. The precordial pain, substernal pressure sensation, anginal type of radiation, dyspnea, similarity between Hamman's sign, and a pericardial friction rub, plus the abnormal ECG findings, may result in an incorrect interpretation of the underlying disease.

It is interesting to speculate on the cause of the anginal pain in Case 3 and in other cases that have been reported in the literature. There is little doubt that angina may occur in the absence of any pathologic lesion in the coronary arteries, and it is probable that gross disease of these vessels was not present, since most of the cases of mediastinal emphysema have been found in relatively young individuals. It seems reasonable to postulate the occurrence of a temporary

functional coronary insufficiency in these cases. This could be affected by one of several mechanisms. Right heart stasis, due to compression of the pulmonary blood-vessels by air in the vascular sheaths, may offer increased resistance to outflow of blood from the coronary vessels, *via* the Thebesian channels and coronary sinus, and lead to decreased coronary flow and myocardial anoxemia. Fisher<sup>2</sup> found dilatation of the right auricle and right ventricle at autopsy in a fatal case of spontaneous pulmonic interstitial and mediastinal emphysema occurring in a newborn infant. Microscopically, the large pulmonary vessels and their smaller ramifications were compressed and flattened by the air in the perivascular sheaths to such an extent as to seriously impede the blood flow through them. Experimentally, it has been demonstrated that an increased intramediastinal pressure has the same effects as increased intrapericardial pressure. If the tension reaches the level of the venous and intra-auricular pressure, the veins and auricles collapse and the circulation of blood stops. It is possible that the air also exerts direct pressure on the coronary vessels through both layers of the pericardium and even causes tamponade of the heart itself.

The demonstration of ECG changes in 3 of the cases is a point of particular interest. A review of the literature reveals no report of similar changes. Several investigators have indicated that mediastinal emphysema may simulate exactly the clinical picture of coronary thrombosis and suggest electrocardiography as an aid in the differential diagnosis of these two conditions. The few ECG studies that have been reported in mediastinal emphysema have revealed no significant abnormalities. Although not diagnostic, the serial ECG changes in our 3 cases, in the presence of clinical symptoms, could easily be mistaken for serious myocardial damage. It is likely that the associated pneumothorax produced these ECG abnormalities. Similar records have been noted in patients in whom a spontaneous pneumothorax simulated coronary disease;<sup>4,9</sup> and several investigators,<sup>5,6,7</sup> have noted that pneumothorax, probably by rotating the cardiac axis, may produce ECG changes suggesting coronary disease. These are most commonly T wave abnormalities, S-T deviation from the iso-electric level and absent or greatly reduced initial deflection in the standard Lead IV ECG.

The combination of pneumothorax with mediastinal emphysema in each of the 4 cases is worthy of comment in view of the obscure etiology of benign spontaneous pneumothorax. One of the most commonly accepted theories is that of a ruptured emphysematous bleb. In his experiments, Macklin was able to demonstrate the formation of such subpleural blebs. This followed the dissection of air out of the perivascular sheaths into the connective tissue and eventually to the pleura. More commonly the air reached the pleural cavity through a rent in the wall of the mediastinum. Experimentally, he found it easy to force air from the mediastinum into the pleural cavity, but not in the reverse direction. Hamman suggests that this mechanism of rupture of the air from the mediastinum into the pleural cavity

may explain the development of some cases of spontaneous pneumothorax better than the theory of ruptured subpleural bleb.

Ordinarily, the pneumothoraces associated with mediastinal emphysema are small and not detected until a roentgenogram of the chest is taken. In the cases being reported, they were large enough to be detected on physical examination. As in the cases previously described in the literature, the pneumothoraces were all on the left side, a fact which has as yet not been adequately explained.

In each of the cases a definite diagnosis was made by detection of the typical sounds (Hamman's sign) over the heart. These sounds may show great variation in intensity and quality during the course of the patient's illness and may last for several weeks. Although it has been stated that the typical sound of mediastinal emphysema is easily differentiated from a pericardial friction rub, the author has noted in 2 of his patients that as Hamman's sign became less marked, it tended to assume the characteristics of a rough pericardial friction rub. This was particularly marked in the prone position. As the patients assumed the upright position, the typical crackling, crunching sounds reappeared.

**Summary.** Spontaneous mediastinal emphysema is briefly discussed with a short review of the pertinent clinical and experimental literature. Four new cases of spontaneous mediastinal emphysema associated with left-sided pneumothorax are described in which the clinical history, physical or ECG examination simulated organic heart disease.

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### A METHOD FOR MEASURING SMALL AMOUNTS OF WEIGHT LOSS IN MAN\*†

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SINCE Sanctorius measured his own weight loss in 1614, there have been many publications of insensible weight loss. The methods used have been reviewed by Benedict and Root<sup>1</sup> and will not be discussed

\* Aided by a grant from the Rockefeller Foundation.

† This is the fifth paper from this Laboratory of Tropical Physiology.

in detail again. The methods have varied considerably in sensitivity as well as practicability. Most of them have been sensitive to 100 gm. The method of Lombard<sup>5</sup> is quite sensitive; the weighted balance responds to 0.02 gm. and the unweighted balance to 0.002 gm. Changes in weight are recorded graphically on a drum by means of a lever which magnifies the movement of the balance 10 times. The apparatus is particularly useful for measuring variations over a very short period of time. The sensitivity of the apparatus reduces its practicability to some extent, especially in long-time experiments. The "silk scales" sensitive to 5 to 10 gm., and the Sauter balance, sensitive to 0.10 gm. used by Benedict and Root, have been employed for prolonged studies of weight loss.<sup>4,6</sup> In the study of insensible loss of weight in infants, suitable adaptations of the ordinary laboratory type chemical balances have been made. Day,<sup>3</sup> for instance, was able to weigh infants with an accuracy of 0.02 gm. with such a balance. These methods have certain disadvantages, however, under many experimental circumstances.

It is the purpose of this report to describe a balance applicable in measuring insensible changes in weight over very short or long periods of time. It can be used as a sensitive balance, that is, sensitive to at least 0.05 gm., or when such a sensitivity is not desired, as in prolonged studies, the sensitivity can be reduced to almost any desired level.

*The Balance.* The balance is illustrated by Figures 1 and 2. The balance as delivered by the manufacturer\* consists of a heavy steel frame which supports the fulcrum and arms above. The subject is suspended by the arm on the right and the weights are suspended by the arm on the left. The ratio of the lever lengths, or weight ratio, is 4:1. The scale as received from the manufacturer is not very simple to use and, therefore, certain modifications are necessary.

Figure 1 is a diagrammatic representation of the modified balance. The various parts are labeled in detail so as to simplify the interpretation of all figures. The balance is mounted as follows:

1. The *air dampers* are made on the principle of the air dampers of the Curie type of commercial chemical balance. These dampers are constructed as shown in insert A, Figure 1. They consist of a group of metal cylinders made of 26 gauge galvanized iron sheeting. The outer cylinder has a diameter of 14 inches, and the succeeding inner ones are made smaller, so that there is  $\frac{3}{8}$  inch clearance between the walls of all of them. *a''* and *b''* (insert A) are cylinders which are entirely enclosed to form pistons. The set of cylinders labeled *a'* and *b'*, and represented by the solid lines (insert A), are clamped to the upper and lower surfaces of the bottom shelf of the weight-bearing end of the balance. The outer group of cylinders labeled *a* and *b* (insert A) and represented by the interrupted line, are so arranged that they may be moved as necessary to avoid any friction between the inner group of cylinders when the weight-bearing end of the balance moves. The rigid arm (C) and wooden platform (*a''*) permit adjustments of the outer group of cylinders.

The dampers bring the balance to a standstill in 6 minutes instead of 23, once it has been set into maximum pendulous vibration.

Other forms of dampers, such as oil containing a paddle fixed to the fulcrum region of the balance, small electromagnets, and so on, were tried, but were found to produce errors or were too cumbersome or complicated.

2. *The Photographic and Recording Portions of the Balance.* To magnify the movements of the balance, to record them photographically for a permanent

\* Buffalo Scale Company, Buffalo, N. Y.

record and to increase the accuracy, the following was constructed: An aluminum plate (*i*) was fixed to the beam of the balance near the main fulcrum and so arranged as to prevent any rubbing of parts when the balance vibrated. A hole was drilled and tapped into the aluminum plate and an aluminum rod ( $\frac{1}{4}$  inch in diameter) screwed into it so that the center of the rod was in the center of the knife edge of the central fulcrum of the beam. The aluminum rod was long enough to extend 3 inches beyond the side frame of the balance. The distal end of the rod held a mirror (*o*) mounted as shown by insert *B*

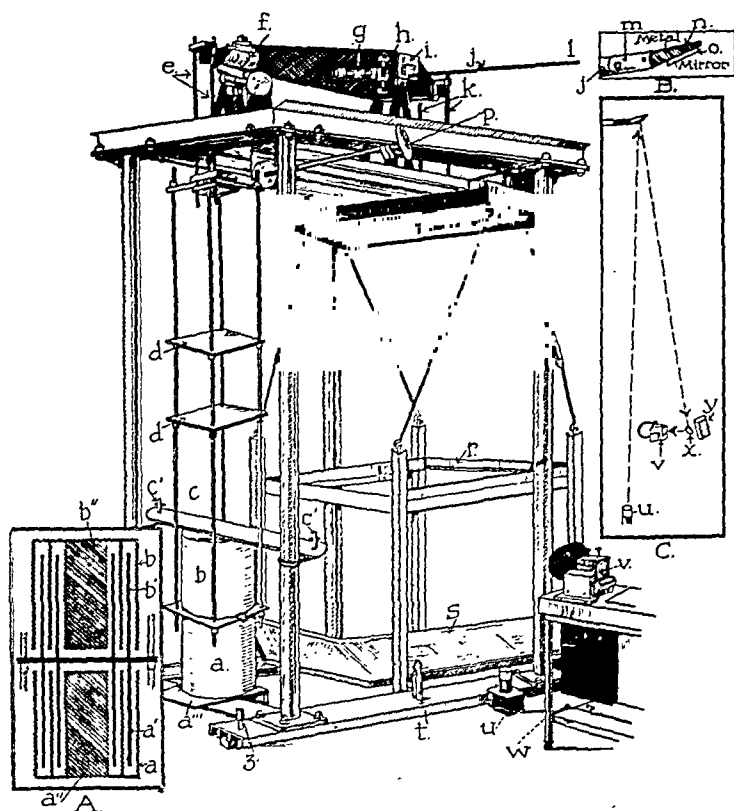


Fig. 1.—Diagrammatic representation of the balance.

*A*, Cross section of the air dampers; *a*, *b*, outer sets of air dampers; *a'*, *b'*, inner sets of air dampers; *c*, *c'*, set of air dampers (*b*); *d*, wing belts for adjusting air dampers (*b*); *e*, rods suspending weight carriage; *f*, underweight for balancing subjects; *g*, *h*, rods for gross adjustments of balance when adding weights; *i*, plate added to balance to support rod (*j*); *j*, rod to support mirror.

*B*, Insert showing details of mirror cemented on end of rod (*j*); *k*, rods suspending frame for subjects; *l*, mirror mount (see insert *B*); *m*, metal segment which permits rotation of mirror (*o*) along transverse axis of rod (*j*); *n*, metal segment which permits rotation of mirror (*o*) along transverse axis of rod (*j*); *o*, concave mirror (focal length 2 meters); *p*, arm for release of balance when weighing; *q*, screw for leveling subject in cot and frame; *r*, angle iron frame which may be used to support other apparatus used simultaneously with weighings; *s*, metal cot made of  $\frac{1}{4}$  inch mesh wire and angle iron; *t*, locks (of which there are 4) used to steady subject's side of balance; *u*, lamp; *v*, camera; *w*, camera table; *x*, plane mirror; *y*, cover for mirror (*z*); *z*, screw for leveling scale.

*C*, Insert showing travel of light beam with camera slit for recording.

(Fig. 1). Aluminum joints (*m*) and (*n*) permitted adjustment of the mirror in any desired direction. The mirror is concave with a focal length of 2 meters. A 21 candle-power 6 volt lamp and housing (*u*) was mounted to the base of the balance near the floor (Figs. 1 and 2). An adjustable slit was made in the housing of the lamp and focussed onto the mirror (*o*). The image of the slit of light was then reflected by a plane mirror to an ordinary electrocardiographic type of camera. The mirror which reflects the light beam into the slit of the camera is mounted on the camera table and covered by a wooden box hinged so that the mirror can be uncovered when the camera is in use by rotating

the box. The top of the box covering the plane mirror is made of 24 gauge stainless steel sheeting with its two side borders turned over so that a sheet of ordinary typewriter paper can be slipped under these edges and held firmly

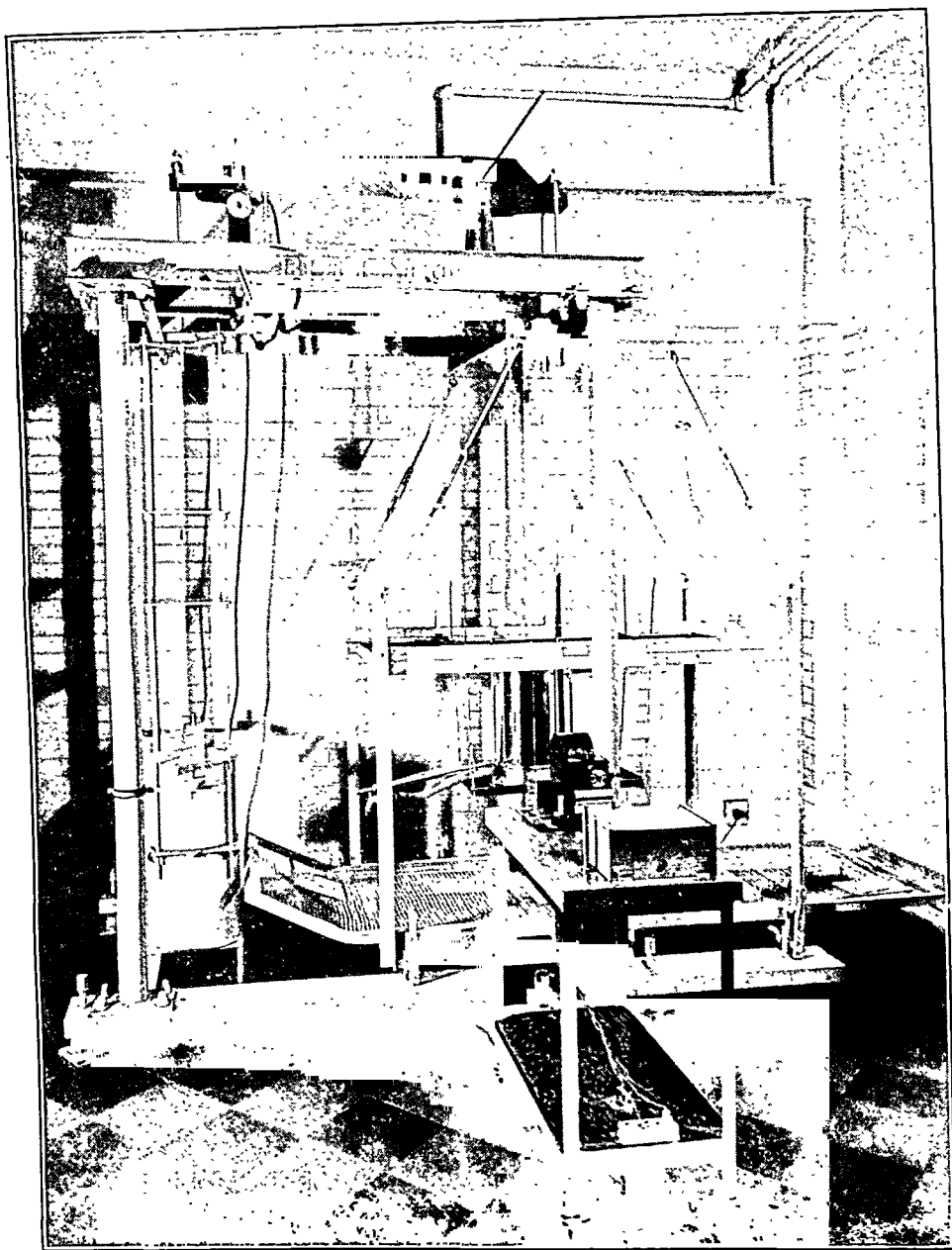


FIG. 2.—The balance and camera table assembled and ready for use. The parts of each are shown in Figure 1 and discussed in the text.

in place on top of the box. When the box is down covering the plane mirror, the light beam reflected from the concave mirror on the balance falls upon the paper on the top of the box, thus making it possible to follow the movement of the balance in a lighted room with a pencil. This is done whenever photographic recordings are not desired. The penciled records on the sheets of paper used on the top of the box may be kept as a permanent record.

An all-metal cot (s) (Figs. 1 and 2) was constructed of angle iron and  $\frac{1}{4}$  inch mesh wire gauze. The cot is placed on the balance as indicated by the figures. Figure 2 shows a basal metabolism machine suspended on the balance so that the basal metabolism rate may be measured simultaneously with the weighing of the subjects. Similar types of large and heavy apparatus may be placed on the balance with the subject for simultaneous measurement of other physiologic processes.

3. *Method of Use of the Balance.* The balance is used in an air-conditioned room, the condition of the atmosphere of the room being maintained at a constant level several hours before and during the weighing of the subjects. The constancy of the conditions of the room prevents a condensation or evaporation of moisture upon, or from parts of the balance during use.

The subjects are made to rest in the supine position on the metal cot. Their arms and legs are abducted in order to facilitate evaporation of moisture from the skin of the axillæ, groin and genitalia. After the subjects have rested on the balance at least 15 minutes, the balance is unlocked and the beam released. Weights are added until the scale is balanced. When it is balanced, the air-condition unit is turned off and the air currents in the room stop almost completely. The balance is rechecked to make certain that it is in balance. The illumination of the room is then reduced so as not to interfere with photography. The slit of light is turned on. The reflected light beam is then reflected into the camera by rotating back the box on the camera table. A record is then made for a desired time, or not longer than it takes for the light beam to traverse the width of the opening in the camera. That requires from 15 to 30 or more minutes, depending upon the rate of weight loss.

To calibrate, the following procedure is employed: Just before completion of the recording, a known weight is added to the subject's side of the balance. This moves the light beam back into the opposite direction a measurable distance, a distance preferably about equal to that traveled by the beam of light when the subject lost his weight. It has been found that either 2, 5 or 10 gm. are necessary, 5 gm. usually being used. This is necessary for each measurement, as the sensitivity of the balance varies with the load. This type of calibration makes it possible to convert millimeters of movement of the light beam on the photographic record into weight loss in grams per unit of time.

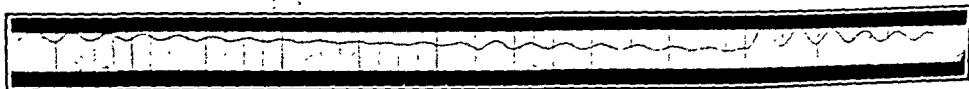


FIG. 3.—An original tracing.

The coarse smooth waves on the horizontal line produced by the light beam from the concave mirror on the balance represents slow pendulous vibrations of the balance due to slight movement by the subject. The very fine waves in the tracing seen on very close inspection are the movements in the balance produced by the respiration of the subject. The sudden rise in the tracing and large smooth waves seen at the terminal portion of the tracing were produced by the addition of 5 gm. to the subject's side of the balance on calibration. The vertical lines in the tracing are timer marks produced by the quarterly minute flashes of the timer light. Each fourth vertical line is darker than the others, thus marking the whole minute.

When prolonged experiments are conducted, such as 24 hour studies, the balance is employed more or less as an ordinary analytical balance, except that a series of weighings can be done with an accuracy of 0.050 gm.

Whenever a short or long study is conducted and a photographic recording is not desired, a penciled record may be made on the top of the box covering the plane mirror on the camera table. This was described in more detail with the description of the camera table and photographic technique (*vide supra*).

The rate of weight loss can be determined for a period as short as a fraction of a minute to any desired period of greater length.

Figure 3 shows a tracing which has been reduced about 10 times in size.

*Accuracy of the Balance.* In the next paper,<sup>2</sup> studies of weight loss were conducted over short periods of time, varying from 10 to 15 minutes. In order to determine the accuracy of the balance as used in these experiments, the following tests were conducted:

A burette containing mercury was placed upon the subject's side of the balance. The tip of the burette was drawn out to a fine capillary opening. The mercury was allowed to drop from the burette at a steady rate of flow and at a rate so that the weight of mercury lost over a period of 15 minutes was approximately the same as the rate of insensible weight loss found in preliminary experiments for normal subjects. A small beaker was suspended and held in place by a clamp under the burette so that the beaker and its support did not touch the balance. The balance was loaded with 150 pounds of steel blocks; that is, a weight equal to that of the average man. During the period of balancing the scale, the mercury was allowed to fall in a beaker placed on the scale under the burette. At the same time that a photographic recording of the change in weight of the balance was started, the previously weighed empty beaker, suspended and not touching the balance, was placed under the burette to catch the dropping mercury. After a period of about 15 minutes, while the recording was in progress, a 2 or a 5 gm. weight was dropped on the side of the balance supporting the burette in order to calibrate the recording as described above. The recording was then stopped simultaneously with the removal of the beaker collecting the mercury that escaped from the burette. By weighing the mercury caught in the beaker on an analytical balance, sensitive to 0.1 mg., the rate of weight loss due to the escape of mercury from the burette was accurately determined. The rate of weight loss was then determined from the photographic record. The balance was found to be accurate to  $\pm 0.150$  gm. per determination, or less than 0.050 gm. for the group of measurements.

**Summary.** The sensitive balance described above for the measurement of changes in weight has many advantages. It is accurate and sensitive. It can be used for prolonged studies, as well as short ones, even as short as a fraction of a minute. The use of photographic recording makes it possible to increase the accuracy and sensitivity of the determinations, as well as providing permanent records. The size of the balance provides for space for the placing of apparatus on the balance with the subjects so that other measurements can be carried out simultaneously with the weighings. It is possible to use the camera, by virtue of its construction, for recording other physiologic phenomena, such as blood pressure, simultaneously with the changes in weight. The nature of the assembly of the balance and photographic apparatus and the construction of the camera table renders the weighing almost automatic. Once the scale is balanced and the photography begun, the recording requires no attention except to place a weight on the subject's side of the balance for the purpose of calibration. The balance as used in the studies described in the succeeding paper



has an accuracy of  $\pm 0.150$  gm. for an individual measurement, or 0.050 gm. for a series of measurements.

I wish to express my appreciation to Mr. G. Morgavi, Jr., for his valuable assistance in the development of the balance.

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### THE RELATION OF TOTAL INSENSIBLE LOSS OF WEIGHT TO WATER LOSS FROM THE SKIN AND LUNGS OF HUMAN SUBJECTS IN A SUBTROPICAL CLIMATE\*†

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THE relationship of insensible water loss from the lungs to that lost from the skin has been studied very little. Many observers have studied the total insensible loss in weight, defined by Isenschmidt<sup>7</sup> by the following equation:

$$I.L. = I.W. + CO_2 - O_2$$

where I.L. represents the insensible loss of weight in grams; I.W. the grams of water vaporized, and  $CO_2$  and  $O_2$  the gaseous exchange in the lungs. I.W. may be further represented as follows:

$$I.W. = I.W._s + I.W._l$$

where  $I.W._s$  represents the water in grams lost insensibly from the skin and  $I.W._l$  that lost insensibly from the lungs. In the normal resting subject, I.W. represents about 93% of I.L.,<sup>8</sup> or the greater part of insensible weight loss is due to insensible water loss. Therefore, in the understanding of insensible weight loss, as well as insensible water loss, the relative values of the water lost insensibly from the lungs and the water lost insensibly from skin is of some importance.

Some observers have published studies conducted to measure such phenomena. Adachi and Ito<sup>1</sup> found their subject to lose 22.52 gm.

\* Aided by a grant in aid from the Rockefeller Foundation.

† This is the sixth paper from this Laboratory of Tropical Physiology.

of water per hour insensibly from the skin, and 5.77 gm. per hour from the lungs when ordinary atmospheric air was inspired. Benedict and Benedict<sup>2</sup> found the water loss from the lungs to be 8.8 gm. to 12.05 gm. per hour, or about 40% of the total insensible water loss. The measurement of water loss from the lungs by Galeotti<sup>6</sup> conform to the results of these groups of observers.

During the course of studying insensible weight loss in subjects living in a subtropical climate, it was deemed advisable to separate insensible water loss from the lungs from that from the skin. The results, although not so different from those of others, were considered appropriate for description.

**Methods and Materials.** The experiments were conducted as follows:

The total weight loss was measured on a special balance<sup>3</sup> which weighs a man with an accuracy of  $\pm 150$  mg., or a series of subjects to an accuracy of 50 mg. The subject rested on a cot suspended from one arm of the balance. The cot was made of a metal screen and frame. Only metal parts were used on the entire balance. Weights were then added to the other arm of the balance. As the subject lost weight, the balance tilted. The degree of rotation was recorded on an electrocardiographic type of camera by a light beam reflected from a mirror properly arranged at the fulcrum of the balance. By means of a suitable timer and the beam of light reflected on the camera, the rate of water loss could be recorded photographically and measured accurately. A continuous recording of total weight loss for a 15 minute period was made for each subject. A Benedict-Roth type of basal metabolism machine was also suspended on the balance slightly above the patient on the patient's side of the balance. The water in the basal metabolism machine was replaced by a heavy mineral oil which was found not to change the weight of the machine by evaporation over periods as long as 24 hours. After recording the total weight loss for 10 to 15 minutes as described above, the B.M.R. machine was properly connected to the patient, filled with oxygen, the scale balanced and then the insensible loss in weight again recorded photographically as before. The change in weight recorded during the period of breathing in the B.M.R. machine represents changes mainly in water through the skin since there are no water or gaseous exchanges made between the lungs and the atmosphere during this time. Any weight lost during this time represents water vaporized from the body surface. The weight lost without the use of the B.M.R. machine minus the weight lost during the period when the B.M.R. machine was in use, was interpreted to represent the insensible weight lost through the lungs. As stated earlier in this paper, insensible weight lost through the lungs is about 93% vaporized water.

In most of the experiments, when the subjects were breathing in the B.M.R. machine, their metabolic rate was recorded on the recording drum.

In order to make certain that there was no change in weight due to: (1) the oil in the B.M.R. machine; (2) the ink used in recording the metabolic rate; (3) the paper used on the drum, or (4) the machine itself, the following experiments were conducted:

1. The scale was balanced with the B.M.R. machine with the oil and containing oxygen and ready for use without a patient on the scale. After 24 hours there was no change in weight.

2. Several pieces of the paper used for the metabolic recording were similarly balanced on the scale. After 24 hours there was no change in weight.

3. Recording paper was inked and then placed on the scale. No weight loss could be detected in 30 minutes.

4. A flat pan, 144 square inches in area, was filled with the heavy mineral oil used in the B.M.R. machine and placed in the scale. After 24 hours the pan did not change in weight.

5. In 7 experiments a "waterless" type of clinical B.M.R. machine was

used instead of the Benedict-Roth type. There was no difference noted in the results of the experiments. The "waterless" machine used was made only of metal and rubber, the bellows being rubber.

Each experiment was conducted as follows: After the room had been conditioned to a temperature of  $75^{\circ}\text{F.} \pm 1^{\circ}$  and a relative humidity of  $50\% \pm 2\%$ , the subjects were brought into the room and made to remove all their clothing, including jewelry. They then reclined in the supine position on the cot suspended from 1 arm of the balance. They were made to abduct their arms and legs so as to permit a more thorough evaporation of water from the axillæ and external genitalia. They were not permitted to rest the forearms and hands on the body; these were rested on the metal cot near to, but not touching the trunk. They rested at least 15 minutes. The forced air currents in the room were stopped by turning off the air-conditioning unit. The scale was blanced by adding the approximate amount of weight to the other arm of the scale. The loss in weight of the subject was recorded graphically as described above. The scale was "locked" and the air-conditioning unit was started again. During the period when the air-conditioning unit was stopped, the room temperature and relative humidity remained within the limits of variations described above. The subject readjusted himself and rested for another 10 to 15 minutes. He was then connected to the B.M.R. machine and a metabolic rate was determined while the loss in weight was recorded. In some instances the weight loss was measured first with the patient breathing in the B.M.R. machine and then with the patient breathing into the room.

When the weighings were made with the subject breathing into the B.M.R. machine, the volume of the B.M.R. machine decreased in volume equal to that of the  $\text{O}_2$  consumed since the  $\text{CO}_2$  expired by the patient was absorbed by soda lime. This decrease in volume of the B.M.R. machine produced a decrease in the buoyant force offered by the air of the room on the B.M.R. machine. This force is equal to the weight of a volume of room air equivalent to the volume of  $\text{O}_2$  consumed during the study. During these weighings the change in buoyant force exerted by the atmosphere increased the weight of the B.M.R. machine. The necessary corrections for buoyance were, therefore, made for each observation.

In order to calibrate the scale so that the beam recorded photographically could be measured as weight loss in grams, the following procedure was followed in each experiment: At the end of the 15 minute period when the insensible weight loss was measured with the subject breathing into the room, a 5 gm. weight was gently dropped on the arm of the scale which suspended the subject. This deflected the light beam a variable amount, usually about 13 mm., varying of course with the weight of the subject. It was then very simple to convert millimeters of movement on the finished photographic tracing to grams of weight loss.

Twelve normal males varying in age from 21 to 33 years of age were studied. One was a Negro and the others white. They were medical students, technicians, and assistants around the laboratory. All of them were trained subjects, having been subjects for many other experiments. The studies were conducted in the afternoon and always more than 2 hours after a relatively small meal. No subject was permitted to drink within 1 hour of the experiment and none of them was thirsty at the time of the experiment. The experiment never lasted over 1 hour and no subject became tired or "restless" during the study.

In another group of studies, 4 subjects were enclosed in a tightly (tested by a water manometer) sealed metal cylindrical tank of 76 inches in length and 30 inches in diameter (Fig. 1). This tank was placed on the subject's side of the balance. The subject rested in the tank and breathed into the outside atmosphere by means of a B.M.R. type of rubber mouthpiece, which opened into the room air through the wall of the tank. The subjects were weighed for total loss in insensible weight before entering the metal cylinder and after being sealed in the cylinder. The conditions of the room air were the same as in the previous group of experiments.

Determinations were also made for the total insensible loss in weight in 10 normal young adult white males and Negro males. All of these subjects have lived in the South all of their lives. The measurement was made on the same days and under similar conditions for both groups of subjects.

The total insensible loss in weight was measured again in 10 normal young white males in the summer\* and winter† months of New Orleans. The room conditions of the laboratory during both seasons were the same as described in the first group of studies.

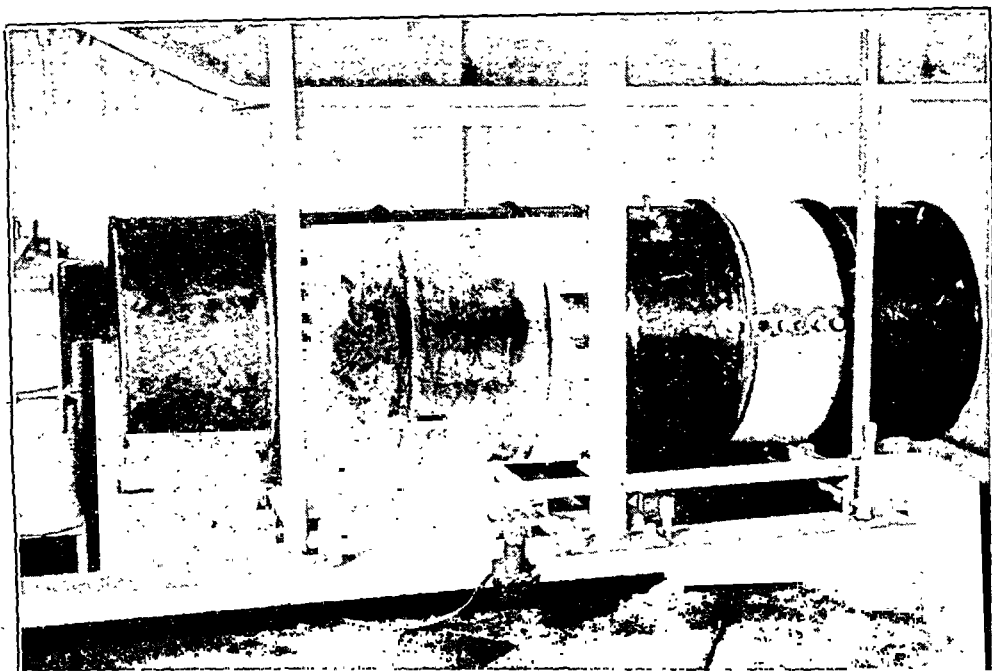


FIG. 1.—A long cylindrical metal tank in which the subjects were enclosed to control water loss through the skin while water loss through the lungs is measured. The photographic apparatus is not shown in place. The metal cot is shown on the balance above the tank. The subjects rested on this cot in order that the total insensible loss in weight could be measured.

Further studies were conducted on the bodies of 10 patients (see Table 5 for details) shortly after death. Only bodies without edema, skin abrasions or signs of dehydration or cachexia were used. The nose, eyelids, mouth, anus, vagina and urethra when opened were closed with sheets of rubber and cellulose tape. The bodies were placed on the balance and the rate of water loss through the skin measured as in the previous studies on living subjects.

In general it may be stated that in all studies the conduction of the observations, care of the subjects and the like, were essentially the same. All values of weight loss were expressed in grams per square meter of surface area per 10 minutes. The values were reduced to units of surface area‡ in order to correct for body size. Ten minutes were used as the unit of time, since the measurements were actually made over periods of about 10 minutes. The values can be easily converted to units of hours or days if necessary. Most of the subjects were studied several times and all living subjects were normal.

\* During August, 1943 the mean temperature and relative humidity were 83.8° F. and 72.3%, respectively. The extremes were 74° and 96° F., and 50 and 100%, respectively.

† During February, 1943 the mean temperature was 57° F. and relative humidity 19.5%, with the extremes 30° and 79° F. and 36 and 100%, respectively.

‡ The surface area was calculated from the height and weight charts of Eugene DuBois and his associates.

**Results.** The results are summarized in Tables 1, 2, 3, 4 and 5.

In the studies conducted on the 12 normal subjects on the balance with and without the use of the B.M.R. machine, the mean rate of total insensible loss in weight was found to be 3.42 gm. per square meter of body surface per 10 minutes,\* with the extremes being 5.50 and 2.40. The mean rate of loss through the lungs was 1.79 and through the skin 1.63 (Table 1). The loss through the lungs was 52.23% of the total insensible loss, that is, with the subjects resting in a comfortable environment the weight lost insensibly through the lungs and through the skin is about equal. This relationship was also essentially true for each individual, as well as for the group, the values varying in absolute amounts but not relatively.

TABLE 1.—INSENSIBLE LOSS IN WEIGHT (GM./M<sup>2</sup>/10 MINUTES) FROM THE SKIN AND LUNGS OF 12 NORMAL ADULT MALES, AGES 23 AND 24, AND ONE 28

Subject No.	Room		Total loss	Skin loss	Lung loss
	Temp. (° C.)	R.H. (%)			
1 . . . . .	23.6	22	3.073	1.708	1.221
2 . . . . .	23.6	43	2.651	1.778	0.873
3 . . . . .	23.6	44	5.503	2.753	2.850
4 . . . . .	22.5	30	4.615	1.746	2.869
5 . . . . .	23.6	46	2.396	0.955	1.441
6 . . . . .	23.6	39	3.045	1.396	1.649
7 . . . . .	23.6	48	2.720	1.690	1.030
8 . . . . .	23.6	55	3.066	1.050	2.016
9 . . . . .	24.6	30	3.226	1.674	1.552
10 . . . . .	23.6	46	2.868	1.310	1.558
11 . . . . .	23.6	55	4.564	1.880	2.684
12 . . . . .	23.6	55	3.335	1.660	1.675
Mean . . . . .	..	..	3.418	1.633	1.785
Max. . . . .	..	..	5.503	2.753	2.869
Min. . . . .	..	..	2.396	0.955	0.873
Per cent of total lost from lungs, 52.23					

TABLE 2.—INSENSIBLE LOSS IN WEIGHT (GM./M<sup>2</sup>/10 MINUTES) IN 4 NORMAL WHITE ADULTS  
(Subjects placed in metal tank to isolate skin)

Subject No.	Total loss	Skin loss	Lung loss
1 . . . . .	2.724	0.600	2.124
2 . . . . .	3.463	1.741	1.722
3 . . . . .	3.038	1.338	1.700
4 . . . . .	1.783	0.668	1.015
Mean . . . . .	2.497	1.087	1.665
Max. . . . .	3.463	1.741	2.124
Min . . . . .	1.783	0.600	1.015

When the subjects were placed in a metal tank so as to control the water loss through the skin, while permitting the loss through the lungs to vary, the results were essentially the same as in the above group of studies (Tables 1 and 2) in which the B.M.R. machine was used to control weight loss through the lungs while weight loss occurred through the skin. There was a tendency for the insensible loss in weight through the lungs to be greater when the tank was used. The

\* Henceforth, for the sake of brevity the unit of measurement will not be repeated since it is the same throughout.

loss through the lungs was 66.6% of the total insensible loss in weight, a difference of 14.4% over the first group of studies.

TABLE 3.—RATE OF INSENSIBLE LOSS OF WEIGHT IN 10 YOUNG NORMAL WHITE AND 10 YOUNG NORMAL NEGRO MALES

(The temperature and relative humidity of the observation room were  $82^{\circ} \pm 1^{\circ} \text{F.}$  and  $60\% \pm 2\%$  respectively)

White					Negro				
Subject No.	Age	Wt. (lbs.)	Surface area (m <sup>2</sup> )	Weight loss (gm./m <sup>2</sup> /10 min.)	Subject No.	Age	Wt. (lbs.)	Surface area (m <sup>2</sup> )	Weight loss (gm./m <sup>2</sup> /10 min.)
1	32	160	1.93	2.282	11	30	127	1.61	3.798
2	22	135	1.76	5.294	12	25	131	1.68	2.069
3	25	178	1.98	7.234	13	20	146	1.69	3.582
4	24	160	1.88	3.612	14	26	145	1.81	3.257
5	24	160	1.85	3.496	15	30	175	1.97	4.144
6	25	156	1.85	1.988	16	38	173	1.95	5.467
7	25	155	1.87	2.934	17	18	118	1.60	1.734
8	23	155	1.88	2.176	18	41	186	2.01	2.579
9	23	130	1.70	3.084	19	32	135	1.73	3.617
10	26	160	1.80	5.019	20	16	140	1.72	5.575
Mean	..	..	..	3.483	Mean	..	..	..	3.582
Max.	..	..	..	7.234	Max.	..	..	..	5.575
Min.	..	..	..	1.988	Min.	..	..	..	1.734

TABLE 4.—COMPARATIVE RATE OF INSENSIBLE LOSS OF WEIGHT IN NORMAL YOUNG WHITE MALES DURING THE SUMMER AND WINTER MONTHS

(The temperature and relative humidity of the observation room were  $75^{\circ} \pm 1^{\circ} \text{F.}$  and  $50\% \pm 2\%$  respectively)

Subject No.	Age	Wt. (lbs.)	Surface area (m <sup>2</sup> )	Total insensible weight loss (gm./m <sup>2</sup> /10 min.)	
				Summer	Winter
10	26	160	1.80	5.218	4.287
21	29	190	2.02	2.442	2.407
22	22	185	2.07	2.994	3.756
23	33	159	1.88	2.986	3.860
24	22	155	1.82	2.921	4.523
25	33	170	1.97	2.529	3.184
26	24	135	1.68	3.570	3.470
27	28	180	1.98	2.549	3.045
28	23	175	1.94	2.294	3.188
29	24	185	2.06	3.548	7.357
Mean	..	..	..	3.105	3.908
Max.	..	..	..	5.218	7.357
Min.	..	..	..	2.294	2.407

The mean rate of total insensible loss in weight in the 10 young white and Negro male adults from the South measured under comparable conditions was 3.48 and 3.59, respectively (Table 3), there being no significant difference. Except for 1 instance (white subject No. 3, Table 3) there was no real difference from individual to individual. In this 1 subject the total insensible loss was over twice that for any individual in the entire group.

The mean rate of total insensible loss in weight in 10 subjects studied under similar laboratory environmental conditions was slightly greater during a cool winter month than a hot summer month, the values being 3.91 and 3.11, respectively. This was true for each individual considered separately except two (Table 4).

The mean rate of water loss through the skin of 10 bodies studied shortly after death was 0.92 (Table 5). The variations were 0.39 and 1.51; the statistical constants are shown in Table 5.

TABLE 5.—LOSS IN WEIGHT (GM./M<sup>2</sup>/10 MINUTES) THROUGH THE SKIN SHORTLY AFTER DEATH FOR ENTIRE BODY

Subject No.	Age	Sex	Color	Room		Hours after death	Weight loss
				Temp. (° C.)	R.H. (%)		
30 . . .	47	M	W	27.2	35	3.5	1.51
31 . . .	49	M	C	27.2	35	2.5	0.87
32 . . .	50	F	C	27.2	37	3.3	0.95
33 . . .	54	F	C	27.4	50	2.5	0.39
34 . . .	59	M	W	25.5	64	2.0	0.71
35 . . .	33	M	C	25.5	36	3.8	1.00
36 . . .	51	F	W	25.5	52	3.6	0.75
37 . . .	26	M	C	25.5	78	6.0	0.93
38 . . .	62	M	C	25.5	78	1.3	1.25
39 . . .	18	M	W	24.0	50	4.0	0.85
Mean	..	..	..	..	..	..	0.92
Max.	..	..	..	..	..	..	1.51
Min.	..	..	..	..	..	..	0.39
Standard error of mean	..	..	..	..	..	..	0.095
Standard deviation	..	..	..	..	..	..	0.302
Standard error of standard deviation	..	..	..	..	..	..	0.068
Coefficient of variation	..	..	..	..	..	..	32.83%
Standard error of coefficient of variation	..	..	..	..	..	..	7.34%

**Discussion.** These experiments were designed primarily to give some insight into the factors making up I.W. and to establish normal values for the subtropical climate of New Orleans. The results were essentially the same as reported by others for different localities,<sup>1,2,8</sup> the main difference being the proportions of water lost through the lungs and skin. In general, less than 30% of the water vapor eliminated insensibly had been estimated to come from the lungs. Adachi and Ito<sup>1</sup> found a loss of 22.52 gm. per hour from the skin and 5.77 from the lungs when ordinarily atmospheric air was breathed. Benedict and Benedict<sup>2</sup> found the loss from the lungs to be about 40% of the total insensible loss. Galeotti<sup>6</sup> published measurements which conform with the latter report. Table 1 shows that our findings agree closely with the latter 2 groups of studies.

When the water loss from the skin was controlled by enclosing the subjects in a tightly sealed metal tank while they were allowed to breathe through an opening in the wall of the tank, the water loss through the lungs was slightly greater than when a B.M.R. machine was used to control water lost through the lungs. Such a difference might be accounted for on the basis of psychic influences on respiration, since the subjects appeared to breathe a little more deeply and rapidly when they were in the metal tank than when on the cot outside the tank. Although all subjects were trained, and repeated measurements were made, they commented on their consciousness of breathing when in the tank. There was very little, if any, rebreathing during the measurements made with the subjects enclosed in the tank, since the length of the tubing including the rubber mouth-piece was only 1 inch in length.

The finding of a similar rate of loss in total insensible weight in the Negro and white subjects is in agreement with the studies of Robinson, Dill, Wilson, and Nielsen.<sup>9</sup> Any racial differences in adaptation to humid heat must be explained by other factors than racial differences due to the dissipation of heat by insensible perspiration.

The greater total insensible water loss in the winter than in the summer months in New Orleans is difficult to explain. Although the environmental conditions of the laboratory were the same during both seasons, the subjects who entered the laboratory during the summer commented upon the coolness of the laboratory. The laboratory was kept at a temperature of 75° F. and the outside temperature was usually in the 90's. In the winter the subjects always found the laboratory warm. At that time the outside temperature was in the 50's or lower, while the laboratory temperature was 75° F. It is possible that a sudden change in the temperature upon entering the laboratory could produce vasoconstrictions in the skin and lungs which might reduce the rate of water loss in the summer. The reverse effects would theoretically be true in the winter. It is also possible that these sudden changes in the conditions of the environment influenced the volume of the tidal air. It has been found<sup>5</sup> that the volume of tidal air increases markedly when a subject is moved from a cool and dry atmosphere to a hot and humid one, and the reverse effect is noted when he is moved from a hot and humid atmosphere into a cool one. It is possible that during the summer the volume of tidal air was decreased when the subjects left a humid and hot environment to enter the relatively cool and dry air-conditioned laboratory. It is unlikely that these differences are due to changes in metabolic rate, as it tends to change very little if at all in tropical climates at least.<sup>10</sup>

The rate of water loss through the bodies shortly after death averaged 0.92. This was water lost entirely through the skin. The mean value for living skin was 1.63. Such a difference might be due to an additional loss through the skin of living subjects by slow imperceptible sweating which was probably absent in the dead bodies. Studies on isolated areas of skin carried out in this laboratory,<sup>4</sup> however, showed that the rate of water loss through dead and living skin (with the subjects resting quietly in a comfortable room) maintained at the same temperature was essentially equal. When the temperature of the skin was lowered, the rate of water loss decreased more or less directly proportional to the change in temperature. In the present studies the skin of the living subjects was at a higher temperature than that of the dead bodies, the temperature of the skin of the latter being about atmospheric. Since most of the water lost through the skin under the conditions of the above experiments was lost by diffusion,<sup>4</sup> most of these differences in water loss through the skin of the living and dead bodies can be accounted for upon the basis of the differences in the effects of skin temperature upon the rate of diffusion.

It is well to emphasize that the above measurements show the skin to be an effective barrier to the loss of water from the body. This has



been indicated previously<sup>4,11</sup> for isolated small areas of dead and living skin. It was found that the skin is a very efficient inhibitor to diffusion of water from the body. The corneum was found to be the layer endowed with the greatest ability to inhibit loss of water by diffusion.<sup>11</sup>

**Summary.** The mean rate of total insensible loss in weight for 12 normal young white adult males living in the subtropical climate of New Orleans was found to be 3.42 gm. per square meter of surface area per 10 minutes. The mean rate of insensible weight loss through the skin was 1.63 and through the lungs 1.79. The latter represents 52.2% of the total insensible loss in weight. The values conform essentially with those reported by other observers for different areas of the world.

The mean rate of total insensible weight loss was found to be the same for 10 young white and 10 young Negro normal adult males. Any differences in the adaptability of the two races to hot and humid environments must not be related to cooling by insensible perspiration.

In 10 normal young white adult males, the mean rate of total insensible weight loss was definitely greater during the cool month of February in New Orleans than the hot humid month of August. Possible explanations for these seasonal variations are offered.

The insensible water loss through the skin of 10 dead bodies studied shortly after death showed a mean rate of loss in weight of 0.92. This is considered to be mainly loss by diffusion through the skin. The lower temperature of the skin of the dead bodies most probably explains the slower rate of loss of water through the skin of the dead bodies than that through the skin of the living ones.

The skin is an efficient inhibitor of the loss of water by diffusion.

We wish to express our appreciation to Mr. G. Morgavi for his keen interest in and contributions to these studies.

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USE OF POSTERIOR PITUITARY EXTRACT IN TESTS OF  
URINARY CONCENTRATION

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MEASUREMENT of the maximal ability of the kidneys to concentrate urine has long been recognized as a most valuable clinical estimate of renal efficiency. Its worth has not been reflected in sufficiently wide application. One reason for its relatively infrequent use is that it requires restriction of fluid or controls of food and fluid for 12 to 72 hours, which impose discomfort on patients. In an effort to circumvent these disadvantages Brunn,<sup>4</sup> (1921) Sodeman and Engelhardt<sup>11</sup> (1941), and Wall<sup>14</sup> (1943) administered subcutaneously posterior pituitary extract with the hope that its antidiuretic action would stimulate maximal urinary concentration during the succeeding short period. Their results were encouraging. However, substitutes for a procedure which has repeatedly demonstrated its accuracy and usefulness must be carefully evaluated before they are introduced into general usage. Our study was designed to compare the merits of the Addis test of urinary concentrating power with those in which pituitary extract was injected with or without periods of fluid deprivation:

**Methods.** Four series of concentration tests were made on 33 normal and 65 abnormal subjects. The abnormal persons were suffering from essential or malignant hypertension, chronic glomerular nephritis, or chronic pyelonephritis. The measurements of specific gravity were made with the Westphal-Van Slyke balance. The temperature of all specimens was adjusted to 20° C. and corrected for protein content (Alving and Van Slyke,<sup>2</sup> 1934). Where the samples were too small for this method, the determination was made pyknometrically.

The first test used was that devised by Addis<sup>1</sup> (1926). In it fluid is restricted for 24 hours. The specific gravity of the urine sample collected during the second 12-hour period was measured.

In a second series, 19 normal and 12 abnormal persons received 10 units of surgical pituitrin subcutaneously, and the test was conducted in a manner described by Sodeman and Engelhardt<sup>12</sup> (1942). The bladder was emptied, and urine was collected every 30 minutes for 3 hours. The specific gravity was measured with pycnometers of 2 ml. content.

As will be shown in Table 1, this test does not result in as great concentration as that in which fluid is withdrawn for 24 hours. Attempts were therefore made to combine short periods of fluid restriction with the antidiuretic principle of pituitary extracts. Since Stephens<sup>13</sup> had shown that aqueous solutions of pituitary extracts induce maximal antidiuresis only for 4 hours or less, the use of surgical pituitrin was discontinued. Greene and January<sup>6,7</sup> (1940) and Stephens<sup>13</sup> (1940) demonstrated that pitressin suspended in oil resulted in more marked and prolonged (12 to 36 hours) antidiuresis than aqueous solutions of pituitary extracts in both patients and animals with diabetes insipidus. Therefore, pitressin tannate in oil was used in the succeeding experiments.

In the first of these, 8 normal and 11 abnormal persons were given subcutaneous injections of 0.5 cc. of pitressin tannate in oil. The bladder was emptied immediately after the injection and no fluid was taken for 5 hours. The specific gravity of the urine formed during this period was measured. The results fell short of the standards established during the Addis examination. Therefore, the period without fluids was increased to 12 hours in 47 abnormal and 15 normal subjects, pitressin tannate in oil being given as before. As a control of this last procedure, the same subjects collected urine during a period of 12 hours in which no fluid was allowed. The mean and range of specific gravities resulting from these tests were calculated and the standard errors of the means were found after the method described by Bradford Hill.<sup>9</sup>

Comparison of urinary output during pituitrin antidiuresis and water deprivation was made for similar periods. Ten patients were given subcutaneous injections of 0.5 cc. of surgical pituitrin at 4-hour intervals during a 12-hour period. The bladder was emptied at the beginning of the test, and all urine formed was collected. The volume and specific gravity of these specimens were compared with those of the Addis tests performed on the same subjects.

TABLE 1.—NORMAL SUBJECTS

Test used	No. of subjects	Mean max. specific gravity	Lowest specific gravity	Highest specific gravity	Standard error of the mean
Addis fluid restricted 24 hrs.	32	1.0302	1.026	1.032	$\pm 0.000393$
Sodeman and Engelhardt max. specific gravity during 3 hrs. following injection of pituitrin	23	1.0251	1.015	1.033	$\pm 0.00115$
0.5 cc. pitressin in oil plus 5 hrs. dehydration	8	1.019	1.016	1.036	
0.5 cc. pitressin in oil plus 12 hrs. dehydration	15	1.0242	1.012	1.030	
12 hrs. dehydration	12	1.020	1.009	1.029	

In this and succeeding tables, standard error of the mean was calculated after the method of Bradford Hill<sup>9</sup> in those groups large enough to make such determinations significant.

TABLE 2.—ABNORMAL SUBJECTS

	Test Used			
	Sodeman and Engelhardt max. reading during 3 hrs. following injection of pituitrin	0.5 cc. pitressin in oil plus 5 hrs. dehydration	0.5 cc. pitressin in oil plus 12 hrs. dehydration	12 hrs. dehydration
Subjects	18	11	47	30
Mean max. specific gravity	1.0182	1.015	1.0181	1.0172
Lowest specific gravity	1.0115	1.008	1.008	1.006
Highest specific gravity	1.0225	1.023	1.028	1.033
Standard error of the mean	$\pm 0.00081$	..	$\pm 0.00068$	$\pm 0.0011$
Addis test for comparison:				
Mean specific gravity	1.0201	1.016	1.0194	1.0202
Lowest specific gravity	1.014	1.008	1.009	1.015
Highest specific gravity	1.025	1.025	1.026	1.025
Standard error of the mean	$\pm 0.00063$	..	$\pm 0.00061$	$\pm 0.000607$
Cases with difference of 0.003+				
Addis test greater	7	3	19	16
Substitute greater	1	0	4	4

**Results.** Tables 1 and 2 compare the results of the 4 tests of ability of the kidneys to concentrate urine to that of the Addis test. These tests consisted of: (1) injection of 10 units of surgical pituitrin, (2) injection of 0.5 cc. of pitressin tannate in oil followed by 5 hours of fluid deprivation, (3) injection of 0.5 cc. of pitressin tannate in oil followed by 12 hours of fluid deprivation, and (4) 12 hours of fluid deprivation. Table 3 compares the output and specific gravities of urine formed by 12 patients during each of two 12-hour periods of antidiuresis: (1) that induced by water deprivation of the Addis test, and (2) that induced by subcutaneous injections of 0.5 cc. of surgical pituitrin every 4 hours.

Among the normal subjects the differences among the various tests were striking. In the first in which surgical pituitrin was given

without fluid restriction the mean specific gravity was 1.025 as compared to the mean of 1.030 in the Addis test. These averages do not reflect the irregular pattern of results, since the range following pituitrin injections was 1.015 and 1.033 and the standard error of the mean  $\pm 0.0011$ , while the range was 1.026 to 1.032 in the control Addis examinations and the standard error of the mean only  $\pm 0.00039$ .

Five hours of fluid deprivation combined with injection of pitressin in oil yielded urine samples, the mean specific gravity of which was 1.019 with a range of 1.016 to 1.036. The mean value following 12 hours fluid deprivation and pitressin tannate was 1.024, and the range 1.012 to 1.030. Fluid starvation alone (12 hours) yielded urine samples with mean specific gravity of 1.020, and the range 1.009 to 1.029.

The same 4 tests gave equally erratic results among the abnormal subjects. The specific gravities of the Addis tests of the first group averaged 1.020 and ranged 1.014 to 1.025, with a standard error of the mean of  $\pm 0.00063$ . Injection of surgical pituitrin was associated with concentrating ability that averaged 1.018 and ranged from 1.011 to 1.022. The standard error of the mean for this group was  $\pm 0.00081$ . Results of the second test, which combined 5 hours of fluid deprivation and injection of pitressin in oil, averaged 1.015 and ranged from 1.008 to 1.023, comparing favorably to the mean of the Addis test, 1.016 (range 1.008 to 1.025). However, this slight difference assumes significance in the presence of renal disease extensive enough to depress concentrating ability to this degree. Further, in 3 of 11 cases the Addis test gave readings 0.003 or more greater than the experimental procedure while none of the latter were superior.

Combination of 12 hours of fluid restriction and injection of pitressin in oil caused an average concentration of 1.018 with a range from 1.008 to 1.028. The standard error of the mean was  $\pm 0.00068$ . Results of the Addis tests of this same group averaged only slightly higher, 1.019. However, in 19 of 47 cases, the results of the Addis test were 0.003 or more greater than those of the experimental procedure, and the standard error of the mean was slightly less,  $\pm 0.00061$ .

Deprivation of fluid for 12 hours resulted in specific gravities that ranged from 1.006 to 1.033 and averaged 1.017, as compared to the mean value of the Addis test of 1.020 (range 1.015 to 1.025). The Addis test gave readings of 0.003 or greater in 16 of 30 subjects, and the standard error of the mean of the Addis tests was  $\pm 0.000607$ , as compared to  $\pm 0.0011$ .

In 4 of 47 patients, the combination of pitressin tannate in oil and 12 hours of fluid was associated with the formation of urine, the specific gravity of which was 0.003 or more greater than that collected following 24 hours of fluid deprivation, and in 4 of 30 cases 12 hours of fluid deprivation alone caused greater concentration. However, these 4 patients underwent the 3 tests on 3 successive days in the following order: Addis test, 12 hours fluid deprivation, and 12 hours fluid deprivation with subcutaneous injection of 0.5 cc. of pitressin tannate in oil. The procedures were thus separated by only 12 hours of normal fluid intake. The results may have been altered in the

direction of increasing urinary concentration by the succeeding periods of abstinence from fluid.

As indicated in Table 3, the outputs of urine resulting from anti-diuresis induced in the same subjects by pituitrin and by water deprivation varied in an unpredictable manner. In 3 cases the injection of pituitrin reduced urine formation to the same degree as restriction of water. The specific gravities of these 3 specimens equalled or exceeded that of the Addis test. However, among the remaining 7 subjects, the results were inconstant. The urinary outputs during the pituitrin-induced antidiuresis varied between 40 and 300% greater than that during the Addis test, and the specific gravities of the samples were 0.004 to 0.014 lower.

TABLE 3.—URINE CONCENTRATIONS WITH THE ADDIS AND PITUITRIN TESTS

	Volume and specific gravity of urine formed during last 12 hrs. of Addis test		Volume and specific gravity of urine formed during a 12 hr. period of pituitrin antidiuresis	
	Volume (cc.)	Specific gravity	Volume (cc.)	Specific gravity
1 . . . . .	680	1.015	1425	1.0115
2 . . . . .	230	1.019	740	1.013
3 . . . . .	525	1.025	1610	1.011
4 . . . . .	275	1.028	420	1.024
5 . . . . .	180	1.024	470	1.0195
6 . . . . .	440	1.016	430	1.016
7 . . . . .	640	1.019	600	1.0204
8 . . . . .	320	1.026	460	1.027
9 . . . . .	230	1.026	440	1.022
10 . . . . .	180	1.029	190	1.027
Average . . . . .	370	1.0217	678.5	1.0192

Pituitrin, in addition to its antidiuretic quality, is known to stimulate smooth muscle. This action was unpleasantly manifested in some of those patients who received as little as 10 units of surgical pituitrin. Seventeen of 41 persons complained of gastro-intestinal symptoms, ranging from abdominal cramps and frequent stools to incapacitating diarrhea. Five of the 41 subjects mentioned tightness in and about the precordium, but found no difficulty in carrying on normal activity. Other side effects of less consequence were pallor, giddiness and excessive perspiration. No reactions followed the use of pitressin tannate in oil.

**Discussion.** The accuracy of the Addis test of ability of kidneys to concentrate urine has been well documented by its author<sup>1</sup> (1926) and by Alying and Van Slyke<sup>2</sup> (1934), and has been used in this clinic for many years. Its value and reproducibility are attested by comparison of specific gravity measurements thus obtained with an independent tubular function, that of secretory capacity for diodrast. A quantitative interpretation of maximal urinary specific gravity has been provided by Corcoran and Page<sup>5</sup> (1942). They reasoned that concentrating ability should parallel tubular secretory capacity as measured by diodrast Tm and that it should be inversely proportional to a function of filtration rate as measured by inulin or urea clearance. They were able to demonstrate such a relationship, and developed a formula

whereby tubular secretory capacity could be predicted from specific gravity and urea clearance. Among patients with renal disease, and especially those with hypertension, the estimation of tubular function thus provided is of great significance. A substitute for an established concentration test should not be accepted unless it is equally reliable and neither more unpleasant nor hazardous to the patient than the older Addis procedure.

Shorter periods of fluid restriction, the injection of antidiuretic pituitary extract alone or in conjunction with short periods of abstinence from fluid, failed in our observation to promote the concentration of urine by normal persons to the same degree as did the Addis test (mean 1.025 compared to 1.030). If these tests had induced a consistent, albeit lower degree of urinary concentration, they might have been acceptable. However, among the normal subjects who received surgical pituitrin, the maximum specific gravity ranged from 1.015 to 1.033, as compared to a range of 1.026 to 1.032 following 24 hours of fluid deprivation. This discrepancy persisted in all tests in which pituitary extract or shorter periods of fluid deprivation were employed.

Injection of surgical pituitrin often produced such side reactions as skin blanching, abdominal cramps and diarrhea, at least as disagreeable as deprivation of fluid for 24 hours. A feeling of constriction about the chest occurred in 5 of 41 patients and called to mind the intense coronary vasoconstriction demonstrated in dogs following injection of pituitrin (Anrep and Stacey,<sup>3</sup> 1927, Gruber and Kountz,<sup>8</sup> 1930, Melville,<sup>10</sup> 1933, and Wegria, Essex, Herrick and Mann,<sup>15</sup> 1940). Temporary reduction of coronary blood flow through diseased vessels might precipitate thrombosis, myocardial injury, or serious cardiac irregularity. It is apparent that fluid deprivation does not endanger the hypertensive patient as may injection of surgical pituitrin.

**Summary and Discussion.** The ability of 33 normal and 65 abnormal persons to concentrate urine was measured by the Addis test, which necessitates water deprivation for 24 hours. These results were compared with those from the same patients in whom pituitrin, pitressin in oil, short periods of dehydration, and combinations of these were made in the hope that a less disagreeable test might be devised. None of these procedures attained the mean concentration of 1.030 recorded after 24 hours' dehydration in normal subjects. The range of variation in them was from 1.016 to 1.033, as compared to 1.026 and 1.032 in the Addis examination. Similar variability was observed in abnormal subjects receiving pituitary extracts.

It is concluded that substitutes for the Addis test which do not approximate the ceiling of specific gravity are not entirely acceptable in clinical practice.

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## SOMATIC PAIN

### DIAGNOSTIC AND THERAPEUTIC ASPECTS OF LOCAL INFILTRATION

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THE use of regional block and local infiltrations to control somatic pain by means of anesthetic preparations has become widespread and the majority of reports is favorable. Application of this method yields excellent therapeutic results. The success or failure of regional infiltration depends on many factors, such as the nature and location of the lesion, the proper localization for infiltration, knowledge of pain pathways, the technique of injection, the interpretation of effects immediately following infiltration, factors which aggravate or prolong the pain, and the psychology and pain sensitivity of the patient.

Somatic pain, as a rule, is less difficult to interpret than visceral pain, so that usually an orderly approach can be made. One of the most valuable assets in determining the origin of somatic pain is knowledge of tenderness and its characteristics.

*Tenderness.* Tenderness is the main factor in determining whether an injection should be given locally, or whether a paravertebral nerve block should be used. Its pattern usually decides the location and origin of the painful stimuli. Its physical characteristics may indicate whether or not the pain is somatic or sympathetic. Tenderness completes the clinical picture so that attention is not focussed merely to the point of spontaneous pain.

An area may be said to be tender when sufficient stimulus is applied to elicit a painful response, the same stimulus failing to evoke a like response in a control zone, preferably one in a symmetrically identical area on the opposite side of the body.

Though skin tenderness may be mistaken for tenderness of underlying structures, the reverse rarely occurs. In neuralgic zones, especially of the segmental type, the location of the spontaneous pain may simulate pain of visceral origin.<sup>2</sup> This is especially true of the abdominal

wall neuralgias. As segmental neuralgia occurs frequently, it is of value here to discuss skin tenderness.

There are 2 types of skin tenderness: superficial and deep. In the superficial type there is tenderness to pinch when a fold of skin and fat is compressed between the fingers. There is also hyperalgesia of the skin demonstrable by pin-prick or pin-stroke. When pinching the skin in the superficially tender type a definite thickness of fat is usually present (Fig. 1). This type may also be tender to poking.

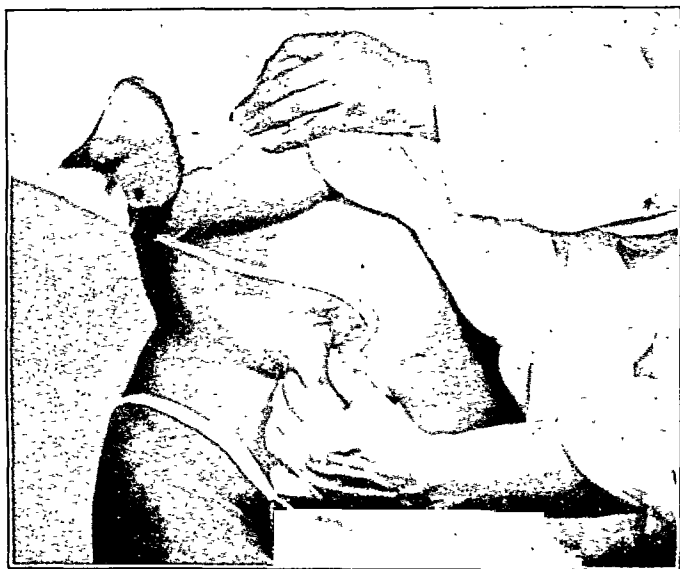


FIG. 1.—Eliciting skin and fat tenderness within a zone of segmental neuralgia. A liberal fold of skin and fat is compressed between the thumb and forefinger. Compare space between thumb and forefinger with that of Figure 2. It is in this type of skin, with the thick fat layer, that we usually find compression tenderness, poke tenderness, and tenderness to pin-stroke. (Judovich and Bates, *Segmental Neuralgia in Painful Syndromes*; courtesy of F. A. Davis Company.)

The second type, deep skin tenderness, is elicited only by poking or pressing the skin firmly against a muscle or bony structure and not by pinching nor by pin-stroke. When the skin is picked up between the fingers and pinched, there is little or no subcutaneous fat in the skin fold (Fig. 2). This type may be defined as pressure tenderness.

The tenderness in both the superficial and deep types follows an identical pattern as to area of distribution. To show that deep skin tenderness is in no way due to underlying muscle sensitivity, certain nerves were selected in areas where the skin and the underlying muscles each received a totally different nerve supply. For example, the distribution of  $D_{12}$  and  $L_1$  nerves overlap the gluteus maximus muscle, which is supplied by  $L_4$ ,  $L_5$ ,  $S_1$ , and  $S_2$ . Paravertebral infiltration of  $D_{12}$  and  $L_1$  nerves with 5 cc. of 1 or 2% procaine causes complete disappearance of deep tenderness in the segmental distribution.

Approximately 15% of patients show this deep skin tenderness. The tenderness may be in the deeper layers or in the superficial fascia,



or perhaps poking stimulates a different type of reaction. In this group, because the patient presents no superficial signs of tenderness, the diagnosis of a neuralgia may be overlooked.

Clinically we have found that interpretation of the origin of somatic pain is facilitated by dividing pain into 3 major groups: local, transmitted and reflex. From the viewpoint of this particular discussion they may be defined as follows:

*Local Pain.* The pain, or pain and tenderness remains confined to the area of involvement. Examples of this type are fibrositis, myositis and tendonitis.



FIG. 2.—Testing the abdominal wall for skin and fat tenderness. Note the close proximity of the thumb and forefinger, which means that little or no fat layer is being compressed. It is in this type of skin that superficial tenderness is absent and deep pressure tenderness present, so that unless tenderness is properly elicited the zone of segmental irritation will be overlooked. (Judovich and Bates, *Segmental Neuralgia in Painful Syndromes*; courtesy of F. A. Davis Company.)

*Transmitted Pain.* The pain is carried along the course of a nerve, with either a segmental or peripheral skin pattern. This implies root or trunk irritation, or irritation in the course of the nerve either by intrinsic nerve changes or irritation by contiguous structures along its course. The pattern of distribution is determined by eliciting tenderness. Examples of this type of pain are the various types of chest and abdominal wall neuralgias, sciatic pain due to root or trunk irritation, occipital neuralgia, and brachial plexus neuralgia. Anesthesia, hypalgesia, hyperalgesia, trophic changes, motor involvement, and diminution or absence of reflexes may or may not be present.

*Reflex Pain.* Reflex pain is pain which is referred from an irritated somatic structure to a distant area within the same segmental innervation. An example of this type is pain which is referred from the hip joint ligaments to the lower leg. The area of referred pain is not asso-

ciated with tenderness. Reflex pain may also be referred from muscles, tendons and other local structures to distant areas of the same segmental innervation or contiguous levels with absence of tenderness in the zone of reference. Sensory, motor, and trophic changes do not involve the area of reference. Reflexes are not affected.

In occasional cases, the area of referred reflex pain may be associated with a markedly sensitive zone which has no neurologic topography and which cannot be classed under the heading of transmitted pain. These areas are probably due to the irritable focus of the lesion sending a bombardment of impulses to the spinal cord, affecting the sympathetic components of that particular segmental level, or contiguous levels, and the resultant irritation is expressed in the periphery by tenderness and pain which is probably vascular in origin.

*Transmitted Pain.* The factor which most often causes confusion in the interpretation and treatment of somatic pain is failure to establish its origin, so that a local infiltration does not produce the desired effect. Errors of this type do not occur often with local pain, but are usually made in the *transmitted type* of pain, often associated with segmental tenderness. In this type, although the source of pain is usually the nerve roots or trunks, the spontaneous pain may develop at any point within the segmental distribution, either in the anterior or posterior divisions. This, of course, is dependent upon which fibers are sufficiently stimulated to reach the pain threshold.

**Case Reports.** The 2 following case reports are used as illustrations of transmitted pain:

CASE 1. S. L., physician, age 48. Chief complaint: Severe low back pain with radiation to anterior thigh. Duration, 7 weeks. Pain and tenderness of the anterior thigh to a point 4 inches above the knee joint. Previous treatment consisted of analgesics, physical therapy, and a sacro-iliac belt. His pain was diagnosed as sacro-iliac in origin. He was unable to wear the belt because of increased discomfort. The points of spontaneous pain involved the upper half of the buttock as far as the sacro-iliac joint medially and the anterior thigh. These areas were within a zone of tenderness which involved the 12th dorsal, 1st and 2nd lumbar dermatomes. There was trunk tenderness paravertebrally at points corresponding to the peripheral distribution. Paravertebral infiltration at these levels caused immediate cessation of pain. There was no recurrence after the first injection 4 years ago. Etiology undetermined.

If this condition had been a sacro-iliac sprain, the radiation which was associated with it should have been lower down, along the branches of the sciatic nerve. These branches, however, were unaffected in this particular case. As a further check, it was found that in the paravertebral level of L<sub>1</sub> and L<sub>2</sub> pressure inward toward the transverse processes caused severe pain. Diagrammatic details are given in Figure 3.

CASE 2. E. C., female, age 45. Complaint: Pain in the left chest, precordium and back. Duration 3 years, with a history of a fall some time previous to the onset of symptoms. Exertion aggravated the pain. Occasionally she developed pain on the left side of the interscapular region. She took "needles" for heart trouble.

Examination revealed segmental tenderness from D<sub>3</sub> to D<sub>8</sub>. There was contralateral tenderness of the dorsolumbar region involving D<sub>12</sub> and L<sub>1</sub> on the right side due to an S scoliosis. There was a  $\frac{1}{2}$  inch shortening of the left leg. A heel raise, with no other form of therapy caused complete cessation of

pain in less than a week. Had this patient not made a recovery with correction of her postural defect, the site of infiltration would have been in the para-vertebral area, selecting those nerve trunks supplying the painful segments. (See Figs. 4 and 5.)

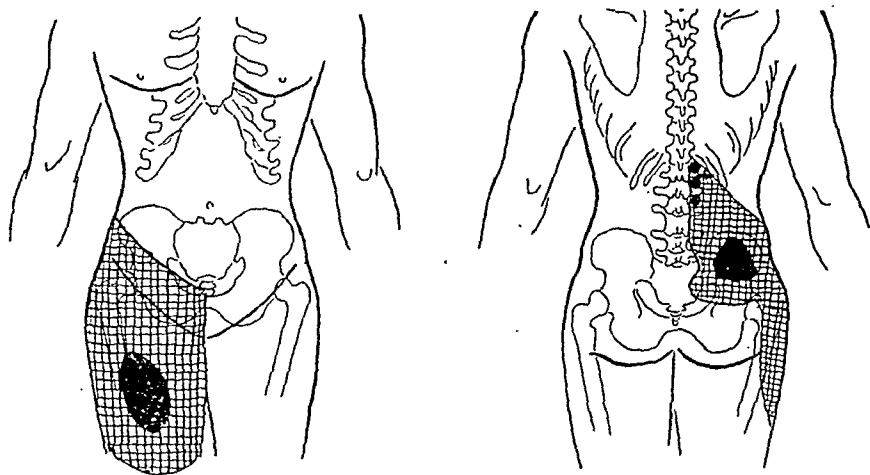


FIG. 3.—(Judovich and Bates, *Segmental Neuralgia in Painful Syndromes*; courtesy of F. A. Davis Company.)



FIG. 4.—Outlined area is the zone of segmental tenderness. The oval areas represent the points of spontaneous pain.



FIG. 5.—Outline shows segmental tenderness posteriorly. Oval area represents area of occasional spontaneous pain. Crosses indicate posterior division tenderness in para-vertebral area.

*Reflex Pain.* The following case serves as an excellent illustration of reflex pain.

CASE 3. M. D., male, age 32. Chief complaint: Severe pain in the right shoulder and arm radiating to the thumb and forefinger. Duration 6 months, with gradual increase in the severity of symptoms. On his initial visit, he stated that his pain was intolerable; it first started over the deltoid muscle, later spread over the clavicle, scapula, neck and to the biceps above the elbow. Two months later it radiated to the thumb and forefinger. Motion of the right shoulder joint had not become limited until his 5th month of pain. There was some difficulty in adducting the arm to the side of the body, especially against counterpressure. There was no history of injury or other factors which precipitated the onset. He had previously had Roentgen ray studies which were found to be negative. In spite of many forms of therapy, he obtained no relief.

When first examined, he had severe pain of the entire shoulder, arm, forearm, thumb and forefinger. However, none of the painful areas were associated with tenderness, except for a small area the size of a half dollar, above and below the middle of the spine of the right scapula. There was no tenderness along the cervical spine, or the paravertebral area. The scalenus anticus syndrome was absent. The reflexes were normal. Routine blood studies were normal.

Infiltration with procaine of the tender region around the spine of the scapula gave partial relief which lasted only for  $\frac{1}{2}$  hour. Further Roentgen ray studies of the cervical spine in the antero-posterior, lateral and oblique projections showed no abnormalities. There was a small localized area of demineralization in the spinous process of the scapula. After another Roentgen ray and comparison with the scapula on the opposite side, the diagnosis was made of destructive lesion of the scapula, probably a sarcoma.

At operation the region in the spine of the scapula was found to be necrotic and a large mass was found involving the subscapularis muscle. The entire scapula was removed except for the glenoid fossa. This was followed by Roentgen ray therapy. The microscopic diagnosis was osteogenic sarcoma.

The patient was in excellent condition 14 months later. There has been no loss of weight, and no evidence of recurrence.

This is an example of pain being reflexly referred from one somatic structure to distant areas of the same segmental innervation without the presence of tenderness.

*Combined Somatic and Sympathetic Pain.* Another group of cases which may present a confusing clinical picture, is that showing mixed types of pain, somatic and sympathetic. This is usually found in the extremities, especially the upper. Pain of vascular origin may be combined with pain of nerve origin so that the resulting syndrome is difficult to evaluate upon an anatomic basis. This is often caused by a spastic anterior scalene muscle which is secondarily affected by local shoulder joint lesions such as tendonitis, myositis, fibrositis and bursitis. Superficially, the symptoms might be those of a brachial plexus neuralgia, or of a bursitis or tendinitis associated with it. Yet, neither a brachial plexus block, nor an injection of the bursa or tendon will control the pain, nor will it give the desired diagnostic information. Infiltrating the anterior scalene muscle with procaine, however, will cause relief of pain in the scapular, infraclavicular lower arm and hand. If any other local lesion about the shoulder joint is present, it will not be relieved and it can be more sharply localized, the overlap of

vascular and neuralgic pain and tenderness of the scalenus syndrome having been erased for the time being. Example of mixed types of pain are illustrated in the 2 following cases:

CASE 4. A male, 45 years old, glass blower, complained of severe pain in the left arm and shoulder of 2 years duration. The pain started around the elbow and upper forearm, and was associated with a numb feeling and coldness of the first 2 fingers. The grip was not impaired. For 2 months he has had some stiffness of the neck with pain in the upper scapular and supraclavicular region. The pain had become very intense and he walked the floor every night for several weeks. Lying down would cause terrific pain in the shoulder blade and upper chest. As it became more intense, the pain spread toward the spine around the level of the first and second dorsal vertebrae. Some days the arm felt like a dead weight, "as though it were going to drop off."

Previous treatment consisted of baking and injections of thiamine, with no relief.

*Examination.* Retracting the head to the right caused shoulder and arm pain. Compression of the scalene insertion on the left was very tender as compared to the right. Pressure caused severe intensification of his pain. The upper chest below the clavicle, and the dorsal surface of the upper forearm were tender. There was no tenderness below this point.

Dynamometric reading of the left hand was 100; the right, 140. In spite of the fact that his first two fingers felt cold, numb and tingled, there was no difference of temperature with thermo-couple measurements as compared to the right hand. There were no alterations of skin sensation. The biceps and triceps tendon reflexes responded normally.

Roentgen ray of the cervical and upper dorsal spine was essentially negative. Wassermann test, blood count, blood sugar and blood sedimentation rate were normal.

This case presented typical symptoms of a scalenus anticus syndrome. However, when the scalene muscle was infiltrated with 1.5 cc. of 2% procaine, the neck, shoulder and upper arm pain disappeared in about a minute, but the pain around the elbow and the upper arm, and the "coldness" and numbness of the first 2 fingers persisted. Examination of the elbow revealed a very tender epicondylitis. Rolling the extensor muscle attachments under the thumb in this area, caused tingling of the first 2 fingers. Injection of 3 cc. of 2% procaine into the extensor attachments caused almost immediate disappearance of the pain in the elbow region. The cold sensation and tingling in the first 2 fingers disappeared as soon as the anesthetic took effect. The painful symptoms and paresthesias did not recur. The sensation in the fingers was undoubtedly due to *reflex paresthesia*.

Thus, a group of symptoms which presented all the characteristics of a brachial plexus neuralgia or of a scalenus anticus syndrome, proved to be neither. An accurate diagnosis would have been impossible had not the overlapping scalenus syndrome been first erased from the picture.

CASE 5. Another example of mixed pain was a patient with controlled diabetes, who complained bitterly of pain in the entire lower extremity. The pain was associated with a burning sensation often described by patients suffering with this disease. Examination revealed a positive Lasègue sign, no atrophy, normal Achilles jerk. The skin of the entire extremity was hyper-sensitive.

Following his first sciatic infiltration, he obtained marked relief of pain. The pain in the anterior thigh and leg persisted. Infiltration of L<sub>2</sub>, L<sub>3</sub>, and L<sub>4</sub> nerve trunks for this distribution gave further relief of the neuralgic pain in this area. Throughout all of his treatment he still complained of the intense

burning sensation on the anterior leg from the knee to the instep. Associated with this was another area on the internal surface of the knee. Neither of these areas had any particular distribution that would suggest either peripheral or segmental nerve involvement. Either by mild or by firm pinching, sharp pain was elicited. However, firm compression of the skin against the bone, with extreme force, caused no pain. In spite of the fact that all trunks from L<sub>2</sub> down had been injected, and his neuralgic pain was definitely relieved, the annoying burning sensation had never subsided. We felt that this pain might be sympathetic in origin.

Following this, L<sub>1</sub> and L<sub>2</sub> sympathetic ganglia were infiltrated, using 5 cc. of 2% procaine at each area. Within a few minutes the burning sensation completely disappeared, with no recurrence reported for several months.

### *Combined Reflex and Transmitted Pain.*

CASE 6. In 1 patient, who complained of severe pain in the back, hip, and leg, we were able to demonstrate both pain and segmental tenderness due to a spinal lesion, and pain without tenderness referred from the hip joint of the same side. The patient stated that the pain traversed the entire leg anteriorly to the front of the ankle, along the course of the anterior crural nerve. Yet upon elicitation of tenderness, a segmental area involving the 3rd lumbar distribution was all that could be found. Here was segmental tenderness associated with the pain of a peripheral distribution without tenderness. The lowermost portion of L<sub>3</sub> distribution ends some distance above the lowermost distribution of the anterior crural nerve and would not account for the pain in the lower anterior leg.

Examination revealed that the spinous processes of L<sub>3</sub> and L<sub>4</sub> vertebræ were very tender to pressure. A positive Patrick's sign was obtained on rotation and abduction of the hip joint. The knee-jerk was absent on the painful side.

Roentgen ray of the spine revealed a marked narrowing of the interspace between L<sub>3</sub> and L<sub>4</sub> vertebræ with bridging of bone. The rest of the lumbar spine was normal. The hip joint showed almost complete destruction of the cartilage, so that the head of the femur rested upon the acetabulum. Thus, we had a spinal lesion with reference of pain to the lower extremity with a definite segmental zone of tenderness and a hip joint lesion with reflex reference along a peripheral nerve which was not associated with tenderness.

Infiltration of the ligaments of the hip joint caused immediate cessation of the pain in the lower third of the leg. The pain just below the knee, however, persisted. Following the infiltration of the 3rd lumbar nerve trunk paravertebrally, this pain was also erased.

*Low Back Pain.* Low back pains may be classified into 2 types: those with radiation, and those without. The radiating pains may be of reflex or transmitted type. Areas which may be affected by radiating pains are the iliac crest, the lower quadrant of the abdomen, and the anterior or posterior aspects of the lower extremity.

The areas of referred pain may or may not be tender. If tenderness is present in a segmental pattern (transmitted pain), it signifies that there is irritation of the roots or trunks and that therapy should be directed to the spinal area. In these cases paravertebral tenderness is found at levels which correspond to the peripheral distribution. Hence, local infiltration or any other therapy applied to peripheral areas of spontaneous pain prove to be of little therapeutic value.

In low back pain without radiation, areas of local tenderness usually can be elicited. Areas frequently involved are the spinous processes, the lumbosacral or sacro-iliac junctions. Soft tissue syndromes such

as myositis and fibrositis are often observed. Tenderness in these areas is usually limited to the particular structure which is irritated. If injection therapy is to be employed, local infiltration should be used. Nerve block will be of little value (Figs. 6 and 7).



FIG. 6.—Pressure or fist percussion over spinous processes causes a painful reaction when applied at levels within a zone of segmental tenderness.

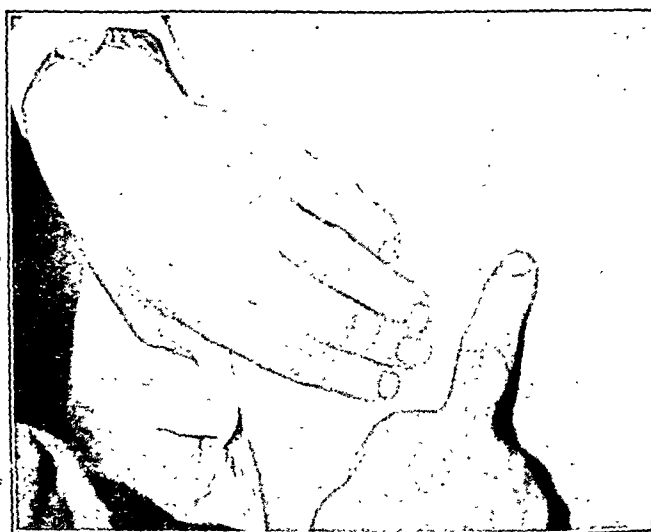


FIG. 7.—Keeping the palpating finger at the same point and pulling the normal skin over to the painful side causes the pain on pressure to disappear, which demonstrates that the tenderness is in the skin and not in the structures beneath.

A local infiltration of procaine into these areas is not always conclusive of the fact that these areas are the cause of the pain. Procaine does curious things. In patients with segmental neuralgia, where we are certain that the irritating focus is either in the spine or in the paravertebral area, a local infiltration of procaine into the peripheral area of pain, even at points in the anterior division, may cause cessa-

tion of pain in the entire segment. However, the patient does not obtain prolonged relief of pain and often has a flare-up following the subsidence of anesthesia. A paravertebral infiltration in the same patient, selecting the involved nerve trunks, yields a much more satisfactory result.

This observation is in accord with those of Livingston,<sup>6</sup> who, in a recent monograph on "Pain Mechanisms," states that he has injected procaine distal to a nerve lesion and secured temporary alleviation of symptoms. He also quotes Mitchell<sup>7</sup> and Tinel's<sup>8</sup> relief of pain by cutting a nerve distal to a known lesion of the nerve trunk causing the pain.

Lewis<sup>4,5</sup> states that, although the hyperalgesia due to local injury may vary in extent according to the degree of injury, it remains within the distribution of a single peripheral nerve, or one of its branches, and never extends into the territory of adjacent nerves. From Lewis' statement, it would appear that a local lesion in the periphery, although it could cause areas of pain reference, would not set up tenderness of a segmental distribution.

In low back pain having its origin at the dorsolumbar area, the patient's complaints may so closely simulate those of sacro-iliac pain that diagnosis may be difficult. If the dorsolumbar irritation affects the lower abdominal quadrants, the pain may simulate pain of any of the underlying viscera.

Many of us are familiar with the story of the laborer, who after heavy lifting suddenly develops acute pain in the groin. He is immediately examined with the expectation of finding a hernia. The examination reveals nothing—just pain; but if we look for it, segmental tenderness will often be found in the distributions of  $D_{12}$  and  $L_1$ . This is as much a back sprain as any condition in which backache is the complaint, except for the fact that the anterior fibers are the ones which develop spontaneous pain.

The fact that many back sprains are associated with segmental pain and tenderness gives us reason to feel that the location of the tissue injury in these cases is deep in the paravertebral area, close to the nerve trunks as they emerge, or intraspinal, as in the case of a ruptured disk. Local injury to muscles, tendons, or ligaments, if it does not irritate the nerve trunks, may cause segmental pain but does not appear to cause segmental tenderness.

Patients who permitted injections of irritant materials into various areas only occasionally developed pain reference of nerve reflex mechanism. For example, 10 patients were injected with 0.5 cc. of 6% sodium chloride intramuscularly (a method reported by Kellgren). In only 1 case did there appear to be pain of nerve reference. This particular patient was injected paraspinaly at the level of the first lumbar vertebra and the injection caused pain to spread through the posterior division of this segment. The pain, however, was not associated with the least bit of tenderness.

The rest of the patients received injections intramuscularly at the site of the gluteal muscle or at different levels in the paravertebral



region. As we have stated, only 1 patient in 10 had referred pain, and this was confined to the posterior division of the segment injected. The other patients had some local pain for 1 to 2 minutes, which spread for only a short distance from the site of injection, not more than 4 or 5 inches, and appeared to be confined to the limits of the muscle. In no case was pain referred to the anterior division. In 4 patients, the area of the interspinous ligaments were injected with the saline solution. In 2 cases pain reference was to the abdominal wall, but in neither case was there segmental skin tenderness associated with the referred pain. In another patient the fascial plane was injected at the level of L<sub>1</sub> paraspinally, according to the technique of Kellgren.<sup>3</sup> Pain reference was obtained in the posterior division of the first lumbar nerve only, and it was not associated with skin tenderness, either deep or superficial.

We have observed anterior nerve reference of pain in patients who received gluteal injections of liver and bismuth. The patients stated that the pain traveled down the leg to the calf. Examination at the time revealed that the area of pain reference was not associated with tenderness.

Differentiating the source of pain according to the presence or absence of tenderness has been a more satisfactory working basis than mere attention to the area of pain. This conclusion is supported by observing and treating patients with old back injuries long after the acute disturbance has subsided. Segmental pain and tenderness may persist for months or years in these cases. Any efforts directed to areas of spontaneous pain in the periphery of the segment are of no avail in clearing up the pain. It is true that local infiltrations will cause temporary cessation of pain, but this is no source of satisfaction to the patient, since it is of short duration and is often followed by an aggravation of pain.

On the other hand, attention being directed to the paravertebral area, infiltration of the nerve trunks responsible for the segmental tenderness causes prolonged relief, often curing the complaint of pain. Chances of permanent relief are further enhanced when existing postural defects are corrected. Commonly a heel lift for a shortened extremity is of great aid. The short leg produces a mild scoliosis, often ignored, but, nevertheless, sufficient to be the cause of the pain. Many of our patients have had pain recur after forgetting to have the heel lifted in new shoes.

This phenomenon is often the explanation of why patients with segmental pain and tenderness of the lower right abdominal quadrant, with pain of months or years duration, are told by their physicians that they are suffering with chronic appendicitis. The patient may wander to an osteopath who, by treating the spine—perhaps baking, massage, and a heel lift—may cause the pain to subside or disappear. We frequently hear such patients state that their "appendicitis" was cured by an osteopath. The original erroneous diagnosis of appendicitis, was of course, to blame.

In segmental pain and tenderness, nerve block has provided more

rapid relief of pain and rehabilitation of the patient than any other single method we have employed. One mechanism by which the pain is relieved in acute sprains was suggested by Leriche, when he advocated local infiltration of procaine for the treatment of sprained ankles. He stated that the swelling and the period of disability were diminished or completely controlled by this method. His concept of local injury is that a vicious cycle is established at the site of injury, incorporating the usual excitor, connector, and effector stimuli; the effector stimulus being transmitted throughout the sympathetic system. Thus, when a sprain takes place, the stimuli from the point of injury send afferent impulses back along the segment to which they belong. This in turn causes stimulation of the sympathetic efferent fibers, which returns impulses to the vascular system at the point of injury, producing swelling and increased pain.

Whatever the mechanism, it is a fact that the local anesthesia does produce rapid symptomatic relief and shortening of the period of disability, often allowing patients to continue with activity rather than putting the part to rest. Infiltration applied to back sprains acts in the same manner.<sup>1</sup> Often, if the patient is seen and treated soon after the injury, severe pain can be controlled and prolonged disability prevented.

*Failure to Obtain Relief.* Failures should be investigated from several angles. If a paravertebral nerve block does not give relief of pain within 5 minutes and the segmental tenderness still remains, the nerve has not been properly infiltrated.

If the segmental tenderness disappears and the pain still persists, it may be caused by: (1) A lesion proximal to the point of infiltration, which would be intraspinal. (2) A local lesion which is overlapped by a zone of segmental neuralgia. In this event, examination for a local lesion or point of tenderness should be made during the period in which the segmental tenderness has been anesthetized. (3) A visceral lesion which may coexist with the segmental neuralgia. (4) Medico-legal complications, where the patient refuses to admit relief of pain. Malingering will not produce segmental tenderness, but the patient may exaggerate the degree of pain. Hysteria does not produce segmental neuralgia and is usually accompanied by other diagnostic signs. (5) If the patient obtains relief of pain and disappearance of segmental tenderness, and the pain recurs shortly after the anesthesia subsides, an intraspinal lesion must be kept in mind. Many cases of ruptured intervertebral disks have had such a reaction following nerve block. Metastatic lesions of the spine may exist for months without Roentgen ray evidence. The duration of relief is also influenced by the nature of the fluid injected. If the pain is due to a postural defect, injection alone does not usually cause complete control of the pain. Correction of postural defects increases the incidence of permanent relief. Many patients develop pain following an upper respiratory infection, the onset of pain usually developing 1 or 2 weeks later. Unless questioned specifically, this information may not be volunteered by the patient.

Somatic pain may arise from any disease process, toxic absorption or mechanical disturbance which directly or indirectly causes irritation of any of the skeletal structures. In spite of careful search, the causative factors in many cases cannot be discovered.

**Summary and Conclusions.** 1. Tenderness has been stressed as the basis of classifying somatic pain into local, transmitted and reflex types. In the author's experience, this concept has facilitated diagnosis as well as therapy. Case reports have been cited to illustrate its clinical application in each type.

2. Local infiltration and paravertebral nerve block are efficient methods of controlling certain forms of somatic pain. The method is often of value in differential diagnosis. Failure to obtain relief of pain following nerve block may also be of diagnostic value.

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# PROGRESS OF MEDICAL SCIENCE

## SURGERY

UNDER THE CHARGE OF

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## REFRIGERATION IN SURGERY

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THE increased use of reduced temperature in surgery has renewed interest in the effects of temperatures other than those which are considered normal for mammalian tissues. The use of hot or cold applications in surgery is ancient in origin. Despite this fact, the effects of such applications have not been thoroughly understood. The efficacy of heat or cold as therapeutic agents, while recognized, was not well-enough defined to prevent controversy over the temperature which was most useful in any given case. Temperatures low enough to cause freezing or high enough to cause burns were always recognized as pathologic. Therapeutic interest is concerned with the range of temperatures between these extremes. Attempts to affect the course of disease by changing the temperature of the entire body have yielded useful information regarding reactions to heat and cold regardless of the advantages which may have resulted so far as therapy is concerned. Supplementing the excellent observations made by Bazett,<sup>4</sup> careful physiologic observations have been made upon patients undergoing hyperthermia induced for therapeutic reasons.<sup>6,22,23,49</sup> More recently an opportunity for similar studies has been afforded by the introduction of treatment by hypothermia by Fay and Smith<sup>18,46</sup> in 1938. Recent studies of the effects of cold have been made by various authors.<sup>5,7,15,16,20,21,27,28,31,36,41,42,43,45,48</sup>

Cold applications have been frequently used to allay pain in clinical medicine. In fact, the use of cold applications to the right lower quadrant has long been considered a dangerous procedure in cases of acute appendicitis because it decreases the pain and, therefore, may mask the symptoms of a progressing inflammatory process in the appendix. Penetration of the reduced temperature to the inflamed area is not likely<sup>10</sup> and might not be expected to influence the inflammation. The numbing effects of cold have been commonly experienced with the extremities, the nose and the ears being most subject to insensibility from exposure to cold.

Cold applications have been used in superficial inflammatory lesions, frequently without too clear a concept of their effects. There are strong advocates for the application of heat in the treatment of superficial infec-

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tions, and possibly fewer but just as strong advocates for the use of cold. Such controversy is not new. Hot applications up to 40° C. tend to produce a sense of warmth, an increase in cellular activity, and a greater flow of blood to the area; cold, on the other hand, has a tendency to cause opposite effects. Vasoconstriction is found with moderate cold as evidenced by blanching; but vasodilation is also found, especially in colder temperatures.<sup>31</sup> The use of moderately cold applications is useful early to prevent exudation and swelling in non-bacterial inflammation; in infection, cold is likely to do more damage than good because, while it tends to depress the activity of bacteria, it likewise depresses the activity of the tissues and, though it has long been known to inhibit bacterial growth, even freezing temperatures do not kill the common pathogenic organisms. Cold likewise inhibits cellular activity, but freezing causes death of cells. Therefore, if death of the organisms is the aim, little success can be anticipated from cooling infected tissues in the light of the differential response of organisms and tissues to cold. In addition, decreased resistance to infection has been reported to result from cooling.<sup>37</sup>

Studies reported by Large, Bruneau, and Heinbecker indicate that there is delay in the healing of wounds<sup>30</sup> and a greater susceptibility to infection after refrigeration.<sup>13</sup> They found that immersion of dogs' legs in water maintained at 6° C. for 96 hours resulted in edema, depression of motor and sensory function, and degeneration of nerves in the cooled areas. They believe these changes to be due to ischemia. Tissues cooled to 6° C. did not show the usual inflammatory response seen after inoculation of *Strep. hemolyticus*. The number of organisms present remained the same. After the tissues were permitted to warm, there was a decrease in the growth-restricting power of the tissues to the organisms and a more marked inflammatory reaction than usual. Brooks and Duncan<sup>12</sup> also report findings which indicate that in refrigerated tissues there is a more severe inflammation after warming to environmental temperature than was present in areas not subjected to cooling. Many of the experiments of Heinbecker and associates<sup>13,30</sup> were carried out with the limbs immersed in cold water, and thus approximated the conditions responsible for immersion foot in the cases studied by Webster and his associates,<sup>50</sup> and by White.<sup>52</sup> While the tissues might be cooled more effectively in a water bath than when surrounded by ice, and are in a more dependent position than is common in clinical practice, the situations appear otherwise comparable.

The use of artificially induced low temperatures in the treatment of arteriosclerotic gangrene of the lower extremity has been a definite surgical advance. Cooling of a large part of the extremity to temperatures just above freezing is a procedure which was not thought advantageous or possible before the work of Fay and his coworkers<sup>18,46</sup> proved that the human could stand marked lowering of the general body temperature, and indicated that lowered body temperature could be maintained for long periods without obvious damage to normal tissues. These studies, though conceived with the erroneous idea that the course of patients suffering from cancer could be altered beneficially, are important because they renewed interest in the general problem of hypothermia. Allen,<sup>2</sup> in 1939, and Brooks and Duncan,<sup>11</sup> in 1940, demonstrated that necrosis of animal extremities resulting from ischemia occurred after a much longer period of time in the cooled extremity than in the extremity maintained at room temperature. He pointed out that the blood did not clot in the cooled extremity, and that such an extremity was insensitive to pain, so

that amputation without other anesthesia was possible. This knowledge was applied to the problem of the bad risk patient requiring amputation. Allen and his coworkers<sup>3,14</sup> performed amputations under reduced temperature with a tourniquet applied on 45 poor-risk patients with only 7 deaths (15.5%). The authors were impressed with the ease with which the amputations were carried out and the absence of shock in the patients. Numerous reports of the use of the method, especially in arteriosclerotic gangrene, have been enthusiastically presented.<sup>24,25,26,32,35,39,40,44,53</sup> McElvenny<sup>34</sup> reported a case of amputation of both legs for trauma where cooling without a tourniquet was a factor in controlling shock and permitted delay in cleaning up the stumps. While the most obvious application of refrigeration in surgery is that associated with amputation, the method has been applied in other conditions of importance. Probably the most timely is the treatment of immersion foot by cooling of the affected part, which has become the accepted form of therapy.<sup>50,52</sup> Recently Webster<sup>51</sup> has utilized refrigeration for preservation of skin grafts.

It is unfortunate that the term "refrigeration anesthesia" has been applied to the procedure recommended by Allen, for actually the anesthesia afforded is not the most important factor. The tourniquet tightly applied is of great importance in cases where there is likely to be absorption from a gangrenous or badly infected leg. The importance of the tourniquet in this regard is stressed by Maxeiner<sup>33</sup> and by Adolph<sup>1</sup> who reported its use in a case wounded in the Sino-Japanese war.

Important facts which have received too little attention in the past have been more widely appreciated through the interest which Allen's work has stimulated. For years it was an all too general custom to warm legs, the blood supply of which was limited in one way or another. The fact that metabolic needs increased with increase in temperature was well understood, but this fact was not generally considered in treatment of cases of arteriosclerotic gangrene. It is interesting that Starr<sup>47</sup> made the following sage comment in an article describing a thermoregulated heat cradle for use in such limbs: "The considerations which should govern the therapeutic application of heat in peripheral vascular disease are not identical with those which obtain in conditions in which the blood supply is normal. If the vessels are inadequate to carry sufficient blood to meet the increased oxygen demands of heated tissues, positive damage may result from degrees of heat which would be beneficial, were the blood supply more nearly normal. It is well known that 'baking' a foot with undiagnosed peripheral vascular disease may cause gangrene; I have seen 3 instances. The possibility of damage from more moderate overheating may well be greater than has been realized."

Freeman<sup>19</sup> reemphasized this concept with relation to treatment of peripheral vascular disease. During the last war and following it, great emphasis was placed on the application of heat to patients in shock. For years this concept was taught as important in the treatment of shock. Early in the present war, definite evidence of the harmful effects of increased heat in the treatment of shock was presented by Blalock.<sup>8,9</sup> Elman and associates<sup>17</sup> presented data indicating the harmful effects of heat used in the treatment of burns. Lesions in which there is interference to the blood supply are also found to respond poorly to increased temperatures as was so aptly shown by the work of Brooks and Duncan.<sup>11</sup>

While it has been shown that a limb without blood supply will survive longer if cooled, damage does result in time. Even if the part is adequately cooled, the application of a tourniquet presents dangers to survival of

tissue below it if left on for long periods of time. Whether or not the part should be amputated should determine the length of time the tourniquet is allowed to remain.

Brooks and Duncan<sup>11</sup> have reported microscopic changes in ischemic rats' tails even though refrigerated, and warn against too broad clinical use of the tourniquet with refrigeration. They suggest that it is possible that tissue necrosis may result but not be apparent. Richards,<sup>44</sup> in a study of 1 case, believed that he had found evidence of fibrosis of nerve and muscle tissue after ischemia produced by a tourniquet and refrigeration. Large and Heinbecker<sup>29</sup> are of the opinion that the advantages of refrigeration with a tourniquet applied are sufficiently great to eliminate concern over whether or not there is production of anesthesia by means of cold for the amputation. They feel that amputation should be done above the level of the constricting tourniquet and under the usual methods of anesthesia. They do not advocate prolonged cooling of tissues to be preserved because of the delay in wound healing and the lowering of tissue resistance to bacterial invasion. This seems a conservative viewpoint on a sound basis, especially since one of the important advantages of the use of refrigeration and tightly applied tourniquet is that it converts the patient to a better surgical risk.

It is interesting to note the concept concerning the use of cold as presented by Dr. Nancrede to the students at the University of Michigan previous to 1899 in his "Lectures Upon the Principles of Surgery:"<sup>38</sup> "Cold, however, is a most potent remedy when judiciously employed, yet it must not be so intense as to act on the vessels directly through the medium of the overlying tissues, but by impressing the cutaneous nerves and reflexly causing contraction of the vessels. For instance, no amount of cold which could be endured would directly influence the intracranial circulation, hence a moderate degree of cold is all that is requisite. Cold so applied as directly to abstract enough caloric to influence deep seated vessels or those at the center of a more superficial inflammation would lower the cell vitality of the part, favor the cohesion of leucocytes, and diminish ameboid activity. It should therefore, always be employed with caution in parts whose vascularity is normally poor and where decided strangulation of tissue has resulted from extensive and rapid exudation lest stasis be precipitated and gangrene result. When employed in proper cases, cold relieves pain by reducing the hyperemia of the nerves and thus their increased registering power."

Our knowledge of the principles regarding the effects of cold have changed little. Many new facts have been presented with regard to the effects of controlled low temperature, and the reaction of tissues to these temperatures. Clearer concepts regarding the benefit which may be expected from refrigeration are at hand. There is, however, much to be done relating to the determination of the limits of safety and extension of usefulness of refrigeration in surgery.

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## OPHTHALMOLOGY

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## RETINOPATHY IN GLOMERULONEPHRITIS

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CONSIDERABLE confusion still exists concerning the nature, occurrence and mode of development of retinal lesions in cases of glomerulonephritis, especially of the chronic type. This confusion has been due in part, undoubtedly to the persistence among many ophthalmologists of the idea that "albuminuric retinitis" is always evidence of disease of the kidneys and that it never occurs in the absence of renal insufficiency. In other words, the presence of "albuminuric retinitis" is considered in itself to be diagnostic of "chronic nephritis." This idea, however, is becoming less prevalent and the predominant rôle of vascular hypertension in the pro-



duction of the retinopathy is being more generally recognized. This very fact has tended again to confuse the issue as to the incidence and nature of retinal lesions in glomerulonephritis, since many observers think that the lesions are identical with those occurring in primary hypertensive disease and make no attempt to differentiate them. Thus there are two schools of thought, one asserting that all the vascular retinopathies are "renal" and the other that they are "hypertensive" in origin, that is, caused by the elevation of blood pressure in itself.

Two other factors share part of the responsibility for the confusion. Variations in the interpretation of the ophthalmoscopically visible changes and in the terminology used to designate them make it difficult to compare the findings reported by different authors. And last, the difficulties inherent in the clinical diagnosis of chronic glomerulonephritis and its definite differentiation from the terminal stages of primary vascular disease result in considerable uncertainty as to the incidence of the various types of retinal lesions in cases of pure glomerulonephritis. As Ellis states, "A major difficulty in the understanding of Bright's disease is that different renal disorders may, in their late stages, show a very similar clinical picture consisting of hypertension, renal failure, and hypertensive retinitis with papilledema." He adds, "The separation of the various entities is most easily achieved by careful observation of the natural history of their development." It seems probable that the latter statement is particularly true with respect to the differentiation of the retinal pictures characteristic of these different entities.

It was essentially from this viewpoint that I stated in 1935: "In acute glomerulonephritis, as ordinarily seen, retinal changes are not found. Perhaps in most cases, mild retinitis develops at the onset and is characterized by mild hyperemia or ischemia of the disk, some arteriolar constriction, mild edema of the retina and a few flame-shaped hemorrhages in the vicinity of the disk (acute angiospastic retinitis). This retinitis, however, may last only a few days and may leave only slight residuals; thus the majority of patients with acute nephritis will show normal fundi. The fundi remain normal until the terminal stage of the nephritis is heralded, from the ocular standpoint, by the usually sudden appearance of retinitis. During the quiescent period, no changes in the arterioles are visible by means of the ophthalmoscope. The retinitis then develops without preceding arteriolosclerosis and is distinguished by this fact from the retinitis of primary hypertensive disease." Obviously, not all cases of glomerulonephritis run this course, through an acute, a latent, and a terminal period, and the variability of the course in individual cases accounts for much of the variability of the retinal lesions in any particular group of cases. In recognition of this fact, I stated also: "In cases in which there is persistent hypertension with associated retinal arteriolosclerosis following acute nephritis, the residual lesion seems to be generalized progressive vascular disease rather than typical chronic glomerulonephritis; the retinitis which then develops will be of hypertensive rather than nephritic type. When the subject in such a case comes to necropsy, the kidneys present the picture of arteriolosclerosis rather than of terminal glomerulonephritis. Retinal arteriolosclerosis is never an indication of nephritis but only of the diffuse vascular disease which complicates the nephritis." A very similar line of thought was expressed by Friedenwald, also in 1935, when he stated that in retinitis of nephritis, of toxemia of pregnancy, and of malignant hypertension, "there is no essential difference between the retinal lesions which form the picture of albuminuric retinitis."

In essential hypertension "which slowly turns into the malignant form," "the appearance of the retinitis is often sufficiently delayed to allow the development of marked, ophthalmoscopically visible changes in the medium and large-sized retinal vessels prior to the retinitis." Cases of toxemia of pregnancy and of malignant or fulminating nephritis may run their whole course in a few weeks or months and "there is at the outset no ophthalmoscopic evidence of disease of the retinal vessels antecedent to the retinitis."

In the type of acute glomerulonephritis which occurred during the war of 1914-1918 and which was known as "trench nephritis," the ocular fundi were said to show initially slight peripapillary edema and a few hemorrhages in the retina accompanied probably by generalized constriction of the arterioles. These lesions were usually transient and could be attributed either to the general toxic state or, more probably, as suggested by similar changes seen in the ordinary types of acute glomerulonephritis, to the initial rise of blood pressure. Fishberg and Oppenheimer reported 27 cases of "acute and subacute" glomerulonephritis in which the disease was of less than 5 months duration. Hypertension was present in 21 of the 27. In 1 patient there was a malignant hypertensive neuroretinitis. This patient died in 2 months. In 1 case there were choked disks and in 8 cases haziness of the optic disks or constriction of the arteries or both. Fishberg and Oppenheimer stated: "The small incidence of severe retinal lesions in acute glomerulonephritis is probably correlated with the fact that hypertension, the pathogenic factor underlying the retinal lesions, is marked and persistent in only a small part of the cases, though present at one time or another in the large majority of instances. Slight changes notably narrowing of the arteries or haziness of the disk, are found in a considerable proportion of the cases, particularly if the fundus is examined repeatedly. They have no especial prognostic significance. The same is true of the occasional small hemorrhages that are found in the fundi; they may be present in the absence of notable hypertension and are apparently akin to the purpuric spots in the skin that are not uncommon in acute glomerulonephritis." Elwyn states that, in acute diffuse glomerulonephritis, "In the retina the contraction of the arteries is shown by their narrowing, and with it are the signs of acute arteriospastic retinitis, edema, cotton-wool patches and hemorrhages." In his series of 31 cases of acute glomerulonephritis, Gresser stated that only 1 showed retinopathy, which was mild and developed 1 day before death in uremia. It is rather difficult, however, to interpret the other figures given by Gresser in reference to his cases, since he states that 22.5% (7 cases) showed edema of the disk or retina, and that 4 had "hypertensive" and 5 "sclerotic" changes in the retinal vessels. These latter changes could hardly have been due to the nephritis, since the average duration of the disease was given as 2.8 weeks. In the main, as stated by Duke-Elder, "it is generally agreed that in the first attack of acute glomerulonephritis retinopathy does not occur." Therefore, the remainder of this review will deal entirely with chronic glomerulonephritis.

**Pathogenesis.** It is quite generally agreed that the vascular lesions in the retina, generalized and localized constriction of the arterioles and arteriolosclerosis, are directly related to hypertension. Clinically, it seems to be rather definitely established that elevation of blood pressure precedes arteriolosclerosis and is the direct cause of its development. As stated by Ellis, the arteriolar lesion is a direct result of the hypertension, and renal arteriolosclerosis is the result and not the cause of the hyper-

tension. Studies on the hypertension produced in experimental animals by renal ischemia support this view of the development of arteriolosclerosis. Whether constriction of the arterioles precedes or follows the development of hypertension is not so clear, but it is perhaps more logical to assume, with Mosenthal, that peripheral vasoconstriction is secondary to the elevation of the blood pressure.

It is difficult to establish a single or unitarian mechanism for the development of the retinopathy, or rather retinopathies, that occur in glomerulonephritis. "Toxemia" and "arteriosclerosis" have battled back and forth through the years. The conception that retinitis in "nephritis" is due to a disturbance in circulation, to which modern thought may be said to have returned, was advanced first by Traube in 1871. He suggested a secondary increase in tension in the aortic system. In 1863, von Graefe and Schweigger "ascribed the retinal lesions to a generalized disease of the vascular system (arterio-phlebo-sclerosis) which affected the kidney as well" (Duke-Elder), although they had stated in 1860 that the retinitis was due to the toxic action of nitrogenous waste products in the blood. The opinion that the retinopathy was due to local sclerosis in the arteries of the retina was supported especially by Duke Carl of Bavaria (1887) and by von Michel (1899) and in the arteries of the choroid by Cohen (1922). Demonstration by histologic as well as clinical investigations that retinopathy can be present without local arteriosclerosis was furnished by Treitel (1876), Opin and Rochon-Duvigneaud (1903-1904) and Schieck (1907). This led to the more widespread acceptance of the theory that the retinopathy was due to "azotemia" as claimed especially by Rochon-Duvigneaud (1904), Leber (1909), and Widal, Morax and Weill (1910). The theories of increased toxic polypeptides in the blood (Dejean, 1932) and of hypercholesterinemia (Chauffard, 1912) have received less general credence. Clinically, it is difficult to substantiate any of these theories, since it is known that retinopathy is absent in many cases where the values for these substances in the blood are quite high and is present in many instances where the values are normal or low. Verwey in 1927 and Kyrieleis in 1930 were able to demonstrate by fat stains in frozen sections of the retina hyaline lipid degeneration of the walls of the small terminal arterioles. They thought that this was present in all cases of "albuminuric retinitis" and that it was the cause of the lesions in the retina. In the meantime, however, Volhard in 1929 had stated his thesis that increase in blood pressure in itself was the cause of the retinal lesions. He thought that spastic contraction of the arteries resulted in local ischemia and that the resultant anemia and anoxemia caused the ophthalmoscopically and histologically visible lesions in both the vessel walls and in the tissues of the retina. He introduced the term "angiospastic retinitis." Friedenwald confirmed the findings of Verwey and Kyrieleis and expressed his conviction that "albuminuric retinitis is in essence a complication of retinal arteriolar sclerosis." He was willing to accept Volhard's concept of arteriolar spasm but was not willing to accept his conclusion that the arteriolar and the retinal lesions are essentially coincident results of ischemia, since he believed that arteriolar sclerosis and necrosis preceded the development of the retinal lesions proper. He theorized that Volhard's vasopressor substance might be toxic and might directly produce the hyaline degeneration of the smaller vessels, or that transient arteriolar spasm might cause sufficient anoxemia in the tissues of the retina to result in the formation of a trypsin-like substance which could cause the arteriolar lesions. Retinopathy would then occur

as a sequence to the arteriolosclerosis. He called attention to the frequent occurrence of retinal arteriolar sclerosis in chronic glomerulonephritis even when there are no arteriolar lesions in the kidneys or in any other organ. It is well to note, however, that Friedenwald refers to the hyaline lipid degeneration of the terminal arterioles and not to changes in the main branches of the central artery of the retina.

Whatever the exact local mechanism of the development of the retinopathy may be or, as Friedenwald puts it, whatever is "the correct way in which to arrange the progressive order of arterial spasm, arteriolar sclerosis, and retinitis," most authors are now agreed on the close association between hypertension and retinopathy in the various forms of nephritis. The series of cases reported by Fishberg and Oppenheimer, by O'Hare and Cannady, and by Graham, all demonstrate this fact. More recently, Fishberg stated again: "The incidence of retinal lesions in any renal disease strictly parallels the elevation of the blood pressure; moreover, it parallels the elevation of the diastolic, and not the systolic pressure." In a recent discursive article, Elwyn advances his idea of the pathologic physiologic mechanism by which hypertension causes retinopathy. He regards as the common factor in the pathogenesis of the edema, cotton-wool patches, hemorrhages and deposits of hyalin and lipids in any of the vascular retinopathies, the dilatation of the precapillary arterioles, the capillaries and the postcapillary venules consequent to contraction of the small arteries. The resultant slowing of the circulation causes a diminution in the oxygen supply which in turn brings about a softening and increased permeability of the capillary wall. When the arterial contraction is of rapid onset and rather short duration an "acute arteriospastic" retinopathy develops which clears up after relaxation of the contraction. "When the arterial contraction persists for a sufficient time, the retinal tissue remains in a state of chronic deficiency of oxygen. . . . The deposits of hyalin and lipids and the star-shaped figure in the macular area are the result of the deficiency in the supply of oxygen . . . chronic arteriospastic retinitis, or retinopathy."

In the main the histologic changes visible in the retina and choroid do not aid in differentiating the retinopathy occurring in chronic glomerulonephritis from that met with in cases of primary hypertension or in establishing the pathogenesis of the retinopathy. The essential morphologic features of these retinopathies are listed by Friedenwald as: edema of the retina and optic disk; serous, fibrinous, hemorrhagic extravasations in the retina; cytoïd bodies in the nerve fiber layer; flat serous detachment of the retina; arteriolar occlusion and retinal infarction, and secondary and reparative processes, including lipid, especially cholesterol, deposits about the retinal lesion, fat droplet cells, scarring of the retina and glial proliferation, and cystic degeneration. However, Koyanagi adds to these what he considers to be the most characteristic feature of the retinopathy, a lesion of the pigment epithelium of the retina in which the cells become swollen, secrete an excess amount of fluid which accumulates under and infiltrates the retina, and take on active phagocytic properties. Koyanagi does not think that this lesion can be produced by ischemia alone and believes that its presence proves the important part played by some toxic substance in the pathogenesis of the retinopathy. As Duke-Elder sums it up: "It seems of unusual significance that the two most common features in all renal retinopathies are hypertension and attenuated arteries. . . . Most pathologists, however, would not agree that all the changes are the result of a simple ischemia, and would prefer to assume the presence

of two factors—(1) hypertension with ischemia and subsequent malnutrition together with (2) the effect of some toxin or toxins unknown.”

It is unquestionably true that in certain cases of chronic glomerulonephritis it is difficult or impossible to substantiate ophthalmoscopically the assumption that hypertension and arterial or arteriolar constriction are responsible for the lesions seen in the retina. In 1939, Lagrange called attention to the part played by the toxic or “azotemic” anemia of chronic glomerulonephritis in the production of the retinal changes. It was with reference to these cases that I said in 1935: “In most cases of chronic glomerulonephritis the retinitis is of the edematous or vascular type just described. In some cases, however, from the standpoint of the retina, the secondary anemia associated with the renal insufficiency seems to be the dominant factor. In such cases mild retinitis will be seen, hardly distinguishable from that found in pernicious anemia or in anemia secondary to carcinomatosis. The disk is definitely anemic, and scattered superficial cotton-wool patches and hemorrhages, usually of the irregularly round type with white centers, characteristic of anemia are found in a slightly edematous retina. . . . Retinitis of this type is seen only in cases in which the secondary anemia is severe and in which the concentration of hemoglobin is less than 40% (Dare). It is not clear why this retinitis develops in place of the typical retinitis of nephritis.”

**Nomenclature and Clinical Features of the Retinopathy.** Among the earlier authors, all of the retinal lesions occurring in any form of “chronic nephritis” were designated “albuminuric retinitis.” When the distinction between primary or essential hypertension and primary nephritis began to be recognized, the terms retinitis of nephritis or renal retinitis or retinopathy came into vogue for the designation of the retinal lesions of primary nephritis. More recently, names such as “angiospastic” or “ischemic” or “hypertensive” retinitis or retinopathy have been more in favor as indicating the fundamental underlying factor in the production of the retinal lesions. Because of the considerable variation in the retinal pictures presented by individuals in any group of patients with chronic glomerulonephritis, attempts have been made recently by several authors to divide the “retinitis of nephritis” into subgroups, each of which has a somewhat different diagnostic and prognostic significance and perhaps a different pathogenesis.

Fishberg speaks of the occurrence in chronic glomerulonephritis of arteriosclerotic retinopathy and malignant hypertensive retinopathy. By “arteriosclerotic retinopathy” he means hemorrhages and “white spots” due to arteriosclerosis of the retinal arteries. He differentiates this from malignant hypertensive retinopathy by the absence of papilledema and of cotton-wool patches. In “malignant hypertensive retinopathy” papilledema and cotton-wool patches are frequent in addition to the “hard” white spots. “The arterial blood columns are narrowed generally to a striking and sometimes to an extreme degree.” “Arteriosclerosis of the retinal arteries may or may not accompany this form of retinal lesion. In long-standing cases of essential hypertension or chronic glomerulonephritis, evidences of arteriosclerosis are generally present and may be marked.” “In instances in which the hypertension is of brief duration, arteriosclerosis is absent.” Of “arteriosclerotic retinopathy,” Fishberg says: “When well-marked, it is found only where hypertension has existed for a considerable time. . . . The large majority of cases in which the picture occurs are those of essential hypertension. But we have also

seen a considerable number of examples in glomerulonephritis of many years' duration."

O'Hare and Cannady adopted the classification of Fishberg, except that they substituted the term "hypertensive neuroretinopathy" for malignant hypertensive retinopathy. However, in 5 of their patients, they stated that the lesions in the retina progressed from hypertensive retinopathy into a late stage of arteriosclerotic retinopathy and that, in their opinion, these retinopathies were only variations or stages of the same pathologic process. They stated also that there was "no distinctive type of retinal lesion accompanying chronic glomerulonephritis." All but 2 of their 25 patients who eventually developed advanced retinopathy passed through the stage of uncomplicated arteriolar sclerosis, and O'Hare and Cannady believed that the retinal lesions were secondary to primary vascular disease.

Gresser does not use any very definite classification into types of retinopathy but seems to favor descriptions of the ophthalmoscopically visible lesions on the basis of "hypertensive" and "sclerotic" changes in the vessels and "secondary retinal phenomena." This method of recording individual lesions instead of using an inclusive name, if universally employed, would certainly be of more value in estimating the nature and degree of the pathologic processes in any particular case and might ultimately lead to a more uniform interpretation of the abnormal findings. Admittedly, it is more difficult and more subject to misinterpretation in the hands of inexperienced observers than is a general picture diagnosis. For names, Gresser favors "hypertensive retinopathy" and "hypertensive neuroretinopathy."

For designating the retinopathies seen in patients with chronic glomerulonephritis, Graham uses the terms "retinitis of anemia" and "acute angiospastic retinitis." He subdivides the latter into "acute angiospastic retinitis without chronic sclerosis of retinal arterioles" and "acute angiospastic retinitis with chronic sclerosis of retinal arterioles." With the assumption that "acute angiospastic retinitis" includes edema of the retina with or without edema of the optic disks, hemorrhages, cotton-wool patches, and edema residues such as macular stars and the like, the above classification is self-explanatory. The group "acute angiospastic retinitis with chronic sclerosis of retinal arterioles" can be further subdivided, if desired, according to the classification of Keith into "retinitis of diffuse arteriolar disease with hypertension group 3" (without papilledema) and "retinitis of diffuse arteriolar disease with hypertension group 4" (with papilledema—"retinitis of malignant hypertension"). This classification is rather heavy and cumbersome, but it does seem to make possible the presentation of the fundamental characteristics of the retinal lesions in any given case. Under the "retinitis of anemia," Graham included cases with normal retinal vessels and a few cotton-wool patches or hemorrhages in the retina, similar to those seen in cases of severe anemia of non-nephritic origin.

In his discussion of "Arterial Hypertension," Elwyn introduces the terms "acute arteriospastic retinitis" and "chronic arteriospastic retinitis." He states that in the chronic form of diffuse glomerulonephritis, "all possible combinations of the signs of acute and chronic arteriospastic retinitis may be seen in the course of the disease. With the passing of years the signs of aging and of sclerosis of the retinal vessels are added. In the advanced stage of the disease, with high blood pressure, renal insufficiency

and the full-blown picture of acute and chronic spastic retinitis, differentiation between this disease and the malignant stage of essential hypertension may be difficult."

Offhand, there would appear to be little in common between the views of these various authors. But, on closer inspection, it is evident that through the reports of Fishberg, O'Hare and Cannady, Gresser, and Graham, there runs a certain thread of similarity and agreement in spite of the different modes of expression. It becomes obvious that, in the minds of all, the retinopathy usually seen in association with chronic glomerulonephritis is in essence "hypertensive" or "angiospastic" or "ischemic" or "anoxemic" or "arteriosclerotic," which basically are all the same—nutritional; that this retinopathy can occur in the absence of clinical arterial or arteriolar sclerosis and that when arteriolosclerosis is seen in the retina it indicates that diffuse arteriolosclerosis is complicating the glomerulonephritis. Thus, Graham stated that in the 8 patients in his group who showed chronic sclerosis in the retinal arterioles, arteriolosclerosis was found in the kidneys and also in other organs which were examined: heart, liver, pancreas and brain. And Fishberg stated, "In the cases (of retinal arteriolosclerosis or arteriosclerotic retinopathy) that came to necropsy the glomerulonephritis was accompanied by arteriolosclerosis and usually by marked general arteriosclerosis; as is the case in essential hypertension, the retinal arteriosclerosis is but one manifestation of injury to the arteries, and particularly of the arterioles, wrought by long-standing hypertension."

**Incidence and Clinical Significance of Retinopathy.** It is interesting to compare the incidence of retinal lesions in the groups of cases of chronic glomerulonephritis reported by Fishberg and Oppenheimer, O'Hare and Cannady, Gresser, and Graham. In Fishberg and Oppenheimer's series there were 55 cases, 19 of which died under observation. Of the entire group, 41.8% had retinopathy; 73.7% of the cases that died had retinopathy. In O'Hare and Cannady's series there were 32 cases, all with normal ocular fundi or only minimal retinal arteriolar sclerosis at the time of the initial examination, examined repeatedly over an average period of 4 years, and 21 followed until the time of death. Of this group, 78.1% had retinopathy. In Gresser's series there were 50 cases. The number that died under observation is not stated. Of this group, 56% had retinopathy. In Graham's Series 1, there were 56 cases; all died under observation and the diagnosis of chronic glomerulonephritis was confirmed at necropsy. Of this group 82.1% had retinopathy. In Graham's Series 2, there were 50 cases, none of whom died under observation. Of this group, 34% had retinopathy. If the 2 series of Graham are combined, a total of 106 cases, 59.4% had retinopathy. From a comparison of these statistics, it is apparent that retinopathy is a relatively terminal event in chronic glomerulonephritis. Thus, it will be noted that in Graham's Series 2, in which the mortality rate under observation was 0, the incidence of retinopathy was 34%. In Fishberg and Oppenheimer's series, in which the mortality rate was 34.5%, the incidence of retinopathy was 41.8%. In O'Hare and Cannady's series, in which the mortality rate was 65.6%, the incidence of retinopathy was 78.1%. And, in Graham's Series 1, in which the mortality rate was 100%, the incidence of retinopathy was 82.1%. The relatively late development of retinopathy in chronic glomerulonephritis as compared to primary hypertensive disease is probably due to the fact, as noted by Wilson, that "in chronic nephritis severe hypertension is usually a late feature."

Of the 23 cases of retinopathy in Fishberg and Oppenheimer's series, 6 were arteriosclerotic and 17 were hypertensive in type; in O'Hare and Cannady's series, 11 of 25 were arteriosclerotic and 14 were hypertensive; in Graham's combined series, 11 of 63 were anemic and 52 angiospastic or hypertensive in type. Thus, of a total of 111 cases of retinopathy, 83, or 74.7%, were of the hypertensive type. This is further evidence that, in glomerulonephritis, hypertension is the predominant factor in the production of the retinopathy. Since, among the 39 cases of angiospastic retinopathy occurring in his group of necropsy-proven cases, only 8, or 20%, showed definite ophthalmoscopic evidence of arteriolosclerosis, Graham considered "acute angiospastic retinitis without chronic sclerosis of the retinal arterioles" to be the most characteristic retinal lesion in chronic glomerulonephritis.

The question of the occurrence or incidence of sclerosis of the retinal arterioles in chronic glomerulonephritis is one of considerable interest. Eight (14.6%) of Fishberg and Oppenheimer's 55 cases showed uncomplicated retinal arteriolosclerosis as did 5 (15.6%) of O'Hare and Cannady's 32 cases, and 16 (15.1%) of the 106 cases in Graham's combined series. This is a remarkably close agreement by different observers and might well be considered to represent the expected incidence of retinal arteriolosclerosis among cases of chronic glomerulonephritis. The possibility that this figure (approximately 15%) is correct is supported further by the fact that in Graham's Series 1 (necropsy-proven cases) the total incidence of retinal arteriolosclerosis was 14.2% (8 of 56 cases). In all of these cases, retinopathy was present also, which would suggest that all patients who have both diffuse arteriolar disease and glomerulonephritis will develop retinopathy before death. The higher total incidence of retinal arteriolosclerosis in the series of Fishberg and Oppenheimer (no definite figure given) and of O'Hare and Cannady (87.5%) may possibly be explained by the inclusion of angiospastic lesions with the sclerotic lesions of the arterioles. This still leaves unexplained the apparent higher total incidence of retinal arteriolosclerosis in Graham's Series 2 (40%) than in Graham's Series 1 (14.2%). The explanation suggested by Graham, that some of the cases that did not come to necropsy might really have been cases of primary hypertensive disease, is worthy of consideration. However, an alternative explanation may be that the cases of chronic glomerulonephritis in which chronic hypertension and arteriolosclerosis became the outstanding feature rather than progressive renal insufficiency run a longer course and are less likely to reach their terminal phase during a relatively short period of observation. The possibility that the latter explanation may be the correct one is supported somewhat by the fact that the average length of life after the probable onset of the retinopathy in Graham's cases was definitely longer in the group with arteriolosclerosis than in the group without arteriolosclerosis (6.2 months as compared to 4 months).

It is the general impression that all patients with chronic glomerulonephritis will develop retinopathy before death. So that there is a tendency to rule out the diagnosis of chronic glomerulonephritis in a moribund patient if the ocular fundi are normal. However, in Graham's Series 1, the fundi were normal 2 weeks before death in 4 patients, 1 week before death in 2, and 2 days before death in 4. This would suggest the possibility that the fundi may be normal even in the terminal stages in about 20% of patients dying from chronic glomerulonephritis, and consequently that uremia may be due to chronic glomerulonephritis even if no lesions are visible in the



retina. This fact is pointed out also by Fishberg and Oppenheimer. Four of their 18 patients who died in uremia had normal fundi (22 %).

The serious prognostic significance of "albuminuric retinitis" was recognized essentially from the time of its establishment as an entity. Since the separation has been made between chronic glomerulonephritis and essential and malignant hypertension, it has become obvious that life expectancy after the development of retinopathy is even shorter in cases of glomerulonephritis than in cases of malignant hypertension. Thus, Graham found that the mean duration of life after retinopathy developed was 4.3 months in chronic glomerulonephritis as compared to 13 months in malignant hypertension. And O'Hare and Cannady gave the average life expectancy as 6.3 months, with 23 months as the longest duration of life of any patient with retinopathy in their series.

Assuming that a rather rapid rise of the blood pressure above its previous levels is the main factor in the development of the retinopathy, then the reason for the serious prognostic significance of the retinopathy becomes apparent. For, as Wilson states, "It is a common observation that in chronic nephritis, once the blood pressure rises over 200 mm., the patient's condition deteriorates by what may be termed 'geometrical' progression." It is true, however, that an occasional patient with chronic glomerulonephritis will pass successfully through an acute angiospastic episode with retinopathy. The blood pressure will fall, the retinopathy recede, and the patient may remain in relatively good condition for a considerable period of time.

In a study of the "vascular phase" of chronic diffuse glomerulonephritis Horn, Klemperer and Steinberg (*Arch. Int. Med.*, 70, 260, 1942) classified 49 cases into "slowly progressive," "transitional accelerated" and "advanced accelerated" groups on the basis of the type of arteriosclerosis present in the kidneys at necropsy. They stated that narrowing and irregularity in caliber of the retinal arterioles, arteriovenous compression and exudates in the retina were present in all groups. However, the optic discs were normal in all cases of the "slowly progressive" group; while papilledema was present in 62 per cent of the "transitional accelerated" and in 96 per cent of the "advanced accelerated" cases. "It appeared in this study that when severe hypertension had become definitely established, advanced neuroretinopathy either was coexistent or was soon to follow, and further, that it indicated the probable existence of accelerated visceral vascular lesions."

These authors do not think that the lesions in the retina in chronic glomerulonephritis differ in any essential way from those seen in other forms of hypertensive disease. They state: "It is worthy of reëmphasis that the neuroretinopathy of hypertensive patients is in no way induced by the azotemia but is rather the expression of an increased intracranial pressure or is incident to the occurrence of ocular vascular lesions and should be viewed as evidence of the accelerated or malignant phase of hypertension no matter what its basic cause may be. It appears more accurate then, to refer to the full development of this clinical picture in which severe hypertension and papilledema exist as the syndrome of 'malignant hypertension,' possibly associated with accelerated arteriosclerosis, and the presence of all disease entities which are capable of producing this clinical picture should be duly suspected." They think that the height of the blood pressure and the presence of neuroretinopathy are the cardinal clinical criteria for the recognition of the accelerated phase of the arterial complications of chronic glomerulonephritis.

**Comment.** It is apparent from a review such as this that considerable uniformity is being attained in the interpretation of some of the fundamental factors in cardiovascular renal disease and its complications in the retina. It is obvious, however, that there is a great need for the establishment of a more uniform nomenclature of and for more uniform criteria for the diagnosis of vascular disease in the retina.

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## PHYSIOLOGY

## PROCEEDINGS OF

## THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 19, 1944

**Electrical Activity of Acetylcholine at Phase Boundary Between Cholesterol and Saline.** R. BEUTNER and T. CUNLIFFE BARNES\* (Hahnemann Medical College of Philadelphia, Departments of Pharmacology and Physiology). Negative electrical potentials arise through contact of cholesterol or lecithin (dissolved in benzyl alcohol) with acetylcholine and also sympathetic amines.

Benzyl alcohol without addition of a lipid gives no potential with acetylcholine. Unmodified benzyl alcohol gives some potential with the sympathomimetic amines but weaker than if lipid is added to the benzyl alcohol.

These results were obtained with our "oil" cell technique. The decisive experiments are: (1) Pure benzyl alcohol is filled into the "cup" of our "oil" cell. The beaker holding this cup is first filled with saline; acetylcholine added, even as much as 2% (a relatively high concentration), produces no change in the electromotive force. (2) When 0.6% cholesterol

\* The writers wish to express their appreciation to Miss Carol E. Erickson and Mr. Clifford Gilbert for their technical help in this work.

is added to the *benzyl alcohol* in the oil cup an electric negativity appears when acetylcholine is added to the saline solution in the beaker, as the following figures show:

ADDED TO THE AQUEOUS SALINE IN BEAKER	ELECTRIC NEGATIVITY
0.05% acetylcholine	6.0 millivolts
0.10%        "	10.0       "
0.15%       "	14.0       "

(3) Concerning the action of the sympathomimetic amines we used parendrine HCl and benzedrine HCl instead of the unstable epinephrine. Benzyl alcohol without addition gave a potential of 4 mv. when 0.05% parendrine was added to the salt solution. However, benzyl alcohol plus 0.6% cholesterol gave a slightly greater value, *viz.*, 13 mv. Thirty per cent lanolin in benzyl alcohol gave 12 mv. Also tricaproin gave 26 mv. with benzedrine, but no potential at all with 0.05 to 1% acetylcholine. This finding suggests that glycerides are preferably contained in the "adrenergic" fibers being responsible for their response to sympathin.

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**The Importance of Insensible Water Loss in the Metabolism of the Rat.** DAVID M. TENNENT (Merck Institute for Therapeutic Research, Rahway, N. J.). A method is described for the separate determination of the insensible water loss from the skin and from the lungs of individual rats. Three groups of experiments were performed with 5 rats in each group. The rats of the first 2 groups were anesthetized with nembutal or urethane, and the experiments were run at 50% relative humidity and 2 temperature levels. For the first group, at 23° C., the average water loss from the skin was 72% of the total evaporative loss, and for the second group, at 34° C., 73%. The group at 23° suffered a loss of body temperature and had a total water loss which was only one-half that of the group at 34°.

The third group of experiments was performed on non-anesthetized rats at 24° C. The total evaporative loss was the same as that from anesthetized rats that suffered no drop in body temperature, but only 57% of the water came from the skin. This is approximately the same as the amount from human subjects who are not actively sweating. The water loss from the skin of the rat is probably a process of diffusion and evaporation rather than of secretion.

The respiratory volume and the peripheral blood flow, which are under the control of the rat, are more important than environmental factors in determining the insensible water loss. The loss from fed rats is greater than from fasting rats, and the loss is more rapid at night than during the day. Rats at 90° F. and 90% relative humidity lose as much as rats at 74° F. and 50% relative humidity, in spite of the fact that their spontaneous activity is lower.

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**Crystallographic and Optical Properties of Human Hemoglobin. A Proposal for the Standardization of Hemoglobin.\*** DAVID L. DRABKIN (Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). With a view to the development of an acceptable and reliable procedure for the standardization of hemoglobin,

\* Work done under contract with the Office of Scientific Research and Development.

the crystallization of the hemoglobins of different species, including man, was undertaken to secure material suitable for standardization.

*Crystalline Human Hemoglobin.* The preparation of crystalline human hemoglobin in a state suitable for crystallographic characterization does not appear to have been accomplished heretofore. The procedures of Green, Cohn, and Blanchard<sup>6</sup> and Cannan and Redish<sup>1</sup> yield in our hands "crystalline" refractile granules of indefinite shape. Modified procedures have been developed which yield consistently large beautiful crystals of adult human hemoglobin, upon which crystallographic information was readily obtained with the petrographic microscope. The essential step consists in securing suitable concentrated solutions of hemoglobin. Concentration is accomplished by subjecting the original stroma-free solution (obtained from the fresh corpuscles of citrated blood by thorough washing with 1.2% NaCl, containing 0.0025 M  $\text{AlCl}_3$ , dilution with 1 volume of water, and treatment with 2/5 volume of toluene), whose concentration in hemoglobin is of the order of 8 to 10 mM per liter (Mol. Wt. equivalent = 16,700), to dialysis in a refrigerator either against saturated  $(\text{NH}_4)_2\text{SO}_4$  or against 2.8 M phosphate buffer, pH 6.8<sup>6</sup> until the volume of the sac contents is reduced by approximately 45%. Under these conditions 3/4 to 4/5 of the sac contents has precipitated in the form of refractile granules of oxyhemoglobin, which may be considered crystalline, but unsuitable for characterization. The supernatant solution of hemoglobin is removed. The concentration of this solution in hemoglobin is now approximately 13 to 13.5 mM per liter. Crystallization from this solution is accomplished by the cautious addition drop by drop of saturated  $(\text{NH}_4)_2\text{SO}_4$  or the 2.8 M phosphate buffer.

*Crystallographic and Optical Character.* Identical crystals are secured whether  $(\text{NH}_4)_2\text{SO}_4$  or phosphate are used. Crystallization is aided by the use of citrate or oxalate, but crystalline character is not altered by these agents, and crystallization can be accomplished in their absence. Adult human hemoglobin belongs to the *tetragonal* system, and the habit is bipyramidal, with the units in perfectly symmetrical development. The optical character is *negative*, with the characteristic uniaxial diffraction pattern and strong birefringence. The axial ratios are  $a:c = 1:1.263$ . Concentrated solutions prepared from the crystalline material yielded spectrophotometric constants characteristic of unaltered oxyhemoglobin. The most concentrated solution prepared was 38.2 mM per liter, or 63.8 gm. per 100 ml., pH 6.0, the highest concentration yet studied spectrophotometrically in our special 0.007 cm. cuvette.<sup>2</sup>

*Crystalline Myoglobin.* This pigment was prepared in crystalline form from horse and human cardiac muscle by slight modifications in the techniques of Theorell<sup>8</sup> and Morgan<sup>7</sup>. By slow dialysis of solutions against saturated  $(\text{NH}_4)_2\text{SO}_4$  macro-size crystal clusters were obtained in the case of horse metmyoglobin. The crystals are slender *orthorhombic* prisms, with straight extinction. Crystalline human metmyoglobin was obtained for the first time; it too is probably *orthorhombic*.

*Proposal for Standardization of Hemoglobin.* By dialysis of the crystallized material against double distilled water at refrigerator temperature, salt-free solutions of hemoglobin (concentration of 4 to 6.5 mM per liter) and myoglobin were obtained. Upon such solutions the following simultaneous analyses were performed: (1) spectrophotometric determination of total pigment as cyanmethemoglobin, using the constant  $\epsilon(c = 1 \text{ mM per liter, } d = 1 \text{ cm.}) = 11.5$  at wave-length 540 m $\mu$ , previously established on the basis of independent oxygen capacity analyses upon 15 dog bloods;<sup>3</sup>

(2) the photometric determination of iron;<sup>5</sup> (3) the determination of nitrogen. For the hemoglobin of man the respective values are:  $\epsilon = 11.5$ , 0.338% and 17.09%. The amount of Fe in the hemoglobins and myoglobins of man, dog, and horse is remarkably similar (average  $0.339 \pm 0.001$  for hemoglobin, and  $0.340 \pm 0.002$  for myoglobin). Hence, the spectrophotometric constant 11.5 for cyanmethemoglobin (a measure of total pigment) can be used interchangeably in the different species, and the determination of cyanmethemoglobin may be looked upon as equivalent to a determination of hemoglobin or hemin Fe. *Proposal 1* for the standardization of hemoglobin: Determine N upon a salt-free solution prepared as above. Prepare, upon this basis, a cyanmethemoglobin standard. Such standards can be preserved indefinitely. They have been found to undergo no change over a period of more than 6 years.

Protohemin can be prepared readily,<sup>4</sup> and consistently with an Fe content (average of 9 independent preparations =  $8.44 \pm 0.02\%$ ) of 98.5% of theory (8.57%). The spectrum of hemin dicyanide is practically identical<sup>4</sup> with the spectrum of cyanmethemoglobin; the millimolar (Mol. Wt. = 651)  $\epsilon$  value on an Fe basis = 11.3 at 540 m $\mu$ . Hence, a hemin dicyanide solution whose concentration is based upon the amount weighed out  $\times 1.033$  (gravimetric and photometric correction factor from above data) is equivalent photometrically to a cyanmethemoglobin standard. *Proposal 2* for the standardization of hemoglobin: Weigh out a sample of crystalline hemin, dissolve volumetrically in 0.1 to 0.2 M NaOH, and convert to cyanide derivative by addition of excess solid KCN. This yields a *gravimetric standard* equivalent to cyanmethemoglobin, when adjusted as described. Aliquots of cyanmethemoglobin prepared from blood samples can be determined photometrically ("colorimetrically" with appropriate filter) against either or both of the above standards, and may thus be employed in the calibration of any procedure for the quantitation of total hemoglobin.

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**The Nature of Intercalated Disks of Cardiac Muscle Studied by the Microdissection Method.** GEORGE S. DE RENYI (Department of Anatomy, University of Pennsylvania). Pieces of cardiac muscle tissue obtained from various species of mammals were studied in properly balanced physiologic solutions. Intercalated disks were found in fibers responding with contraction to mechanical stimulation. The number, appearance and distribution of this structure in suddenly killed animals has shown no divergence from those in the tissues obtained from other animals dying more slowly. Six hours after death the disks appeared in the same fashion as in the freshly killed animals. The intercalated disks showed resistance to pull, whether it was applied in longitudinal or in transverse direction. It is evident that the substance at the disks is harder than in between. When saline was injected under low pressure into the fiber the

disk prevented the trespass of the liquid from the injected segment to the succeeding one. But the disk broke to parts when the pressure was increased and the saline flowed over into the next segment.

In the course of these studies it became evident that the substance at the disks is considerably harder than the sarcoplasm proper. There was no indication, however, of the existence of a cell membrane at the level of the disk. Conclusion was drawn that the myocardium is a large plasmodium, probably a single multinucleated cell. It is segmented, softer and harder parts alternating, but no cell membranes exist crossing the fibers at any location.

# BOOK REVIEWS AND NOTICES

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THE METHODOLOGY OF PIERRE DUHEM. By ARMAND LOWINGER. Pp. 184. New York: Columbia Univ. Press, 1941. Price, \$2.25.

THE philosophic attitudes of great scientists, especially those who live near the end of an era in scientific thought, are a necessary part of the "evidence" on the basis of which the philosopher of science constructs his theory of experimental method. The scientific mind at the end of an era seems to be more self-conscious of the purposes of science, more reflective upon them, than the mind that finds itself in the midst of a process whose end-point is not at all clear and whose success does not seem to be at all assured.

If this much be so, then the philosopher of science would do well to pay special regard to the writings of Pierre Duhem. He is a genius of a scientific age that had grown optimistic indeed regarding the future of science. Closely analogous to the rationalistic optimism of the seventeenth century concerning the hope of remodeling all science in the framework of the *scientia perfecta*, geometry, was the nineteenth century's optimism towards the future of physics based on the model of the classical mechanics. The attitude, to be sure, was more dynamic in its willingness to admit that basic changes in physical theory might be needed, but there seemed to be no end of possibilities in this direction, and there seemed to be no barrier to the smooth-flowing progress of physical science.

This little book of Mr. Lowinger's is extremely valuable, then, for it represents practically the only complete treatment in English of Duhem's work. In a series of remarkably exhaustive but lucid chapters, Mr. Lowinger constructs the philosophic attitude of Duhem that emanated from the optimism we have described.

As might be expected, Duhem's contribution to the philosophy of theory in experimental science far outweighs what little he has to say on the philosophy of experimental "facts" or data. Indeed, the discussion of "practical" fact *vs.* "theoretical" fact (pp. 96 to 101) in Mr. Lowinger's book leaves the reader wherever he may have started; it repeats a story at least as old as Plato, that the world of sense can never have the character of precision to be found in the world of mathematics. The correspondence of the world of theory and the world of sense is difficult, and apparently the sooner we can leave the latter behind in our reflection on the processes of science, the sooner we can stand on the firm foundations that mathematical theory appears to provide. The story is as old as Plato; its answer much newer. Indeed, it was the adolescent Pragmatism of Duhem's time that was just then struggling to show that the concrete aspects of the world of sense are in reality as much theoretical constructs as are the theorems of mathematics; it was a scarcely yet formulated Experimentalism (E. A. Singer, Jr.) that proposed to consider the "practical fact," not as an immediate datum of sensation, but an ideal of experimental science as impossible to attain, and yet as approachable to attainment, as a completed mechanism.

No, if we are to reap our harvest here, its fruits are to be found in such brilliant insights into the nature of theory as are given in Chap. 8 of Mr. Lowinger's book. It requires a thorough-going formalist such as Duhem was, to see that an experiment designed to test one aspect of nature alone is no experiment at all: "the realization and the interpretation of any physical experiment whatsoever implies adhesion to a whole ensemble of theoretical propositions" (p. 140). This is a lesson that might well serve as a rebuke to some of our contemporary efforts to conduct isolated investigations independent of a general theory.

As for Mr. Lowinger's own reflections on Duhem (Chap. 10), these appear to be born of the newer and more disturbed age in physical theory; far from the optimism of a Poincaré, asserting that the scientist has an "infinite" choice of mechanical theories, Mr. Lowinger feels that "it is with the greatest difficulty that even a single adequate theory can be arrived at" (p. 169).

What is puzzling, though, are the entire series of pronouncements of Mr. Lowinger in this final chapter. Is the author's statement, for example, that methodology is impotent to legislate for science (p. 164) to be taken to mean that a sound statistical methodology cannot legislate the design of an experiment and the inferences therefrom? What Mr. Lowinger calls the "indefeasible facts of the scientific situation" seem to originate in a peculiar and futile attempt to maintain the autonomy of physics, even in those matters that deal with the philosophy of physics: "futile," we say, for one advances in no wise by asserting that "truth" and "reality" are out of place in physics and must be replaced by "fitness and adjustment to the actual scientific process." The meaning of this last phrase is no easier to divine, and its divining belongs no less to a philosophy of physics, than does the meaning of truth and reality.

In a sense, this last chapter might seem to express an opposition to the feeling of calm reflection that lies in Duhem's writings. But this cannot really be the author's intent, to judge from the sympathetic and competent survey contained in the other chapters. Rather, he probably means to sound a note of caution lest the reader stray too far in his enthusiasm from the main point at issue, which is as always the progress of experimental science. C. C.

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A LABORATORY MANUAL OF PHYSIOLOGICAL CHEMISTRY. By D. WRIGHT WILSON, Benjamin Rush Professor of Physiological Chemistry, Univ. of Penna. Pp. 269. Fifth Ed. Baltimore: Williams & Wilkins, 1944. Price, \$2.50.

ARRANGED as a teaching manual for laboratory techniques, this new edition of Wilson's manual is intended to be supplemented by lectures and discussions on the many topics in physiological chemistry which form the basis of understanding of so much modern medicine. There is an introductory section dealing with the chemistry of carbohydrates, fats, and proteins. The main portion of the manual concerns itself with body tissues and fluids. Considerable emphasis is placed on quantitative methods and there is a final chapter describing experiments on dietary deficiencies. W. S.

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THE STANDARDIZATION OF VOLUMETRIC SOLUTIONS. By R. B. BRADSTREET, M.S. Second Ed. Pp. 151; numerous figs. and tables. New York: Chemical Publishing Co., 1944. Price, \$3.75.

THIS book is a small manual, in which are gathered together techniques and discussions of the common volumetric methods. It is intended for the expert analyst. W. S.

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SURFACE CHEMISTRY. Edited by FOREST RAY MOULTON. Pp. 160; many figs. and tables. Washington, D. C.: Amer. Assn. for the Advancement of Science, 1943. Price, to members, \$2.75; to others, \$3.25.

THIS volume comprises a symposium at the University of Chicago participated in by eminent authorities in this highly specialized subject. Beginning some 50 years ago, this field has expanded until now it occupies the full time of many investigators throughout the world. Difficult techniques and detailed theories have been elaborated which form the basis for the understanding of important biologic phenomena. This volume is a survey of current aspects of a difficult field. W. S.



**PRACTICAL METHODS IN BIOCHEMISTRY.** By FREDERICK C. KOCH, Frank P. Hixon Distinguished Service Professor Emeritus of Biochemistry, Univ. of Chicago; Director of Biochemical Research, Armour & Co., Chicago, and MARTIN E. HANKE, Associate Professor of Biochemistry, Univ. of Chicago. Fourth Ed. Pp. 353; 20 figs.; 40 tables. Baltimore: Williams & Wilkins, 1943. Price, \$2.25.

THIS manual is intended for the use of medical students. It is somewhat more than a practical laboratory aid, as it includes a considerable amount of explanatory matter on each topic covered by the experiments. Much can be said for this procedure, for it should serve to correlate more closely the student's theoretical reading with his actual laboratory practice. Some 265 experiments are described covering a very wide range of topics. Mastery of them should form an excellent background for the understanding of clinical chemistry.

W. S.

**THE RADIOLOGY OF BONES AND JOINTS.** By JAMES F. BRAILSFORD, M.D., PH.D., F.R.C.P., F.I.C.S. Third Ed. Pp. 440; 404 ills. Baltimore: Williams & Wilkins, 1944. Price, \$12.00.

THE Third Edition of Dr. Brailsford's book follows very much the pattern established in the earlier editions of this monograph. The book is and has always been valuable because it represents, to a large extent, the analysis of the Author's experience; and in this last edition the Author has continued to bring the various cases reported up to date.

As the author stated in his first edition, this work is one in which each condition described is discussed briefly and in many instances the reviews of other authors have either been quoted or commented upon. The monograph is a valuable contribution to the radiologic literature and is used frequently by most students of radiology.

The paper used is not as good as that used in previous editions and the publisher still uses positive Roentgen ray illustrations rather than negative. It is to be hoped that some day the excellent illustrations provided can be published as negatives, and that after the war, the paper also will be more satisfactory.

E. P.

**ATLAS OF THE BLOOD IN CHILDREN.** By KENNETH D. BLACKFAN, M.D., Late Thomas Morgan Rotch Professor of Pediatrics, Harvard Med. School; Late Physician-in-Chief, Infants' and Children's Hosps., Boston; LOUIS K. DIAMOND, M.D., Assistant Professor of Pediatrics, Harvard Med. School; Visiting Physician and Hematologist, Infants' and Children's Hosps., Boston. With illustrations by C. MERRILL LEISTER, M.D., Associate Pediatrician, St. Luke's Hosp., Bethlehem, and Allentown Gen. Hosp., Allentown, Pa. Pp. 320; 70 ills. in color. New York: Commonwealth Fund, 1944. Price, \$12.00.

WE know of no atlas of the blood in children which will compare with this authoritative and beautifully illustrated volume; and in no medical books are illustrations more important than in a hematological atlas. By the use of high magnifications—mostly well over 1000—the artist, himself a pediatrician, has been able to portray many nuclear and cytoplasmic details without loss of verisimilitude. Opposite each of the 70 polychrome plates is an outline drawing of its cells, each numbered when appropriate, together with a key to facilitate identification; and other notes. The text, which occupies a full first half of the volume, gives "brief descriptions and discussions of various disease entities, including causes, symptoms, morphological variations in the blood; and treatment, with illuminating case histories."

In the consideration of such an excellent work as this, we hope that it will not appear captious to express regret that the text did not go two steps further: (1) to include even a brief consideration of the tissue changes as well as the "laboratory data" (i. e., the peripheral blood changes) of the conditions being considered; and (2) to include in the treatise conditions other than those with

which the authors had "close personal experience." The latter, of course, carries the advantage of being built on a basis of first-hand knowledge, and one readily admits that few if any conditions of great importance appear to be missing.

The volume is the best kind of worthy memorial to Dr. Blackfan, who had planned it many years ago. As Dr. Minot points out in the Foreword, it is of value to all hematologists and internists, as much the same conditions and cells appear in adults as in children, though in different proportions and significances. We are indeed fortunate in having such a worthy volume appear at this time in spite of the necessary war-time restrictions. E. K.

**CLINICAL PRACTICE IN INFECTIOUS DISEASES.** For Students, Practitioners and Medical Officers. By E. H. R. HARRIES, M.D. (Lond.), F.R.C.P., D.P.H., and M. MITMAN, M.D. (Lond.), M.R.C.P., D.P.H., D.M.R.E., with a Foreword by W. ALLEN DALEY, M.D. (Lond.), F.R.C.P., D.P.H. Second Ed. Pp. 570; 26 tables; 52 figs. Great Britain: Williams & Wilkins, 1944. Price, \$6.00.

This is an ideal textbook for the medical student and practitioner. It covers all the infectious diseases, presents about each of them the facts that are of immediate practical importance and omits all theories and procedures that are now discarded. Each chapter begins with a synopsis of its contents, sufficient for a superficial review; the subdivisions of each chapter are indicated in bold type; diagnosis is clarified by illustrations, some of which are colored; tables that help in differential diagnosis are included, and at the end of each chapter is given a bibliography that renders easy access to original contributions. The first few chapters, on infection and resistance, hypersensitiveness and allergy, the transmission of infectious diseases and general clinical manifestations and diagnosis, will be found especially helpful to the student. The place of the sulphonamides in therapy is fully covered and even brief reference to penicillin is made. The newer viewpoint about infective jaundice, including postinoculation jaundice, is adequately described. The Reviewer heartily recommends this book. T. M.

**A NEW GERMAN-ENGLISH PSYCHO-ANALYTICAL VOCABULARY.** Research Supplements to the International Journal of Psycho-Analysis. No. 1. By ALIX STRACHEY. Published for The Institute of Psycho-Analysis. Pp. 84. Baltimore: Williams & Wilkins, 1943. Price, \$2.50.

This small book is an excellent glossary for use by English translators and readers of German psychoanalytic literature. The German terms are well selected and their English translation is brief and satisfactorily complete. J. M.

**CRIME AND THE HUMAN MIND.** By DAVID ABRAHAMSEN, M.D., Department of Psychiatry, Columbia University. With a Foreword by NOLAN D. C. LEWIS, M.D., Director, New York State Psychiatric Inst. and Hosp., Columbia Univ., New York, N. Y. Pp. 244; 3 tables. New York; Columbia Univ. Press, 1944. Price, \$3.00.

With a definitely psychoanalytic coloring, this prolific writer has discussed a timely subject in the following chapters: Criminology as a science; The mind in relation to crime; Heredity and environment as causes of crime; Functional view of the offender; Psychiatric-psychologic examination of the offender; The psychology of the individual offender: classification; Juvenile and war delinquency; The psychiatric-psychologic background of murder; The psychiatric and criminal law; Treatment and research.

Science maintains that heredity determines what we can do, while environment decides that which we do. "This means that a number of men are born to crime, that is their fate when certain constellations are fulfilled." One table gives the rise in delinquent subjects by boroughs in New York City, in the first 5 months of recent years: 1942, 2162; 1943, 2897; 1944, 3066. The more

common juvenile crimes, larceny and burglary; 33.3 and 46.6% respectively, were committed by those under 21 years in 1941; 30 and 29.8% by those between 21 and 29. During the first half of 1941, the percentages were 34 and 48.5 of offenses by those under 21. Most adolescent crimes are petty larceny, burglary, auto theft, and statutory rape. Those of the twenties are chiefly robbery, criminal homicide, embezzlement, and fraud. Forgery is usually an offense of the more mature adult.

In 1943, a report from England told of a 41% increase in delinquency for children under 17. "In addition to this lack of supervision, living in shelters with all types of people during air raids, the blackout with its tempting opportunities for perpetrating crimes, the closing of schools, and the lack of recreational facilities all go far in instigating children to criminal activities." The fallacy of committing those with psychopathic personalities to prison is discussed, where only Federal and a few State penal institutions offer proper treatment. The possibility of homosexuality being regarded as a disease has received no such recognition in the law. In the matter of prostitution, the method employed by Denmark is commended. There, a home has been established on Sprogø Island for the mental defectives and for those on the borderline. After having been taught regular habits, the individuals are removed to places with fewer restrictions; finally, with an appropriate guardian, they are given suitable employment. It is claimed that 80% have later lived satisfactorily, and that about half actually marry.

This experienced writer has contributed a very enlightening book.

N. Y.

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**GYNECOLOGICAL AND OBSTETRICAL UROLOGY.** By HOUSTON S. EVERETT, A.B., A.M., M.D., Associate Professor of Gynecology, Johns Hopkins Univ.; Associate in Gynecology, Univ. of Maryland; Assistant Visiting Gynecologist and Gynecologist in charge of the Cystoscopic Clinic, Johns Hopkins Hosp.; Visiting Gynecologist, Church Home and Hosp., Hosp. for the Women of Maryland, and Union Memorial Hosp. Pp. 517; 220 figs. Baltimore: Williams & Wilkins, 1944. Price, \$6.00.

THE Author's wide personal experience in gynecology and female urology, as head of the female cystoscopic clinic at the Johns Hopkins Hospital, qualifies him for the task of presenting a single volume treatise on urologic problems in the female. Stress is placed on the general nature of urologic disease and its relation to general medicine and the specialties, rather than on the technique of urologic surgery. However the operative techniques of several urologic procedures are presented in detail.

There are chapters on anatomy, physiology; relation of female urology to general medicine, gynecology, and obstetrics; and cystoscopic technique. The latter is entirely the Kelly method.

With this background, the author goes into the diseases of the lower urinary tract, including urethra and bladder. He next discusses incontinence of urine, retention of urine, and diversion of the urinary stream. The upper urinary tract is covered by chapters on congenital anomalies of the kidneys and ureters, ureteral obstructions, hydronephrosis, tuberculosis, non-specific infection, calculus, neoplasm, and traumatic injury.

The book is well organized and covers its intended subject adequately. Illustrations are excellent. It should be of value to medical students, gynecologists, obstetricians, surgeons, and urologists.

L. LA T.

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**PHYSIOLOGY IN HEALTH AND DISEASE.** By CARL J. WIGGERS, M.D., D.Sc., F.A.C.P., Professor of Physiology and Director of Physiology Dept. in the School of Med. of Western Reserve Univ., Cleveland, Ohio. Fourth Ed. Pp. 1174; 274 figs. Philadelphia: Lea & Febiger, 1944. Price, \$10.00.

FIVE years have elapsed since the appearance of the Third Edition of this well-known textbook. The presence in the Fourth Edition of 2 new chapters

on aviation physiology; 1 on hemorrhage and shock; and the increased attention devoted to such subjects as dark adaptation, camouflage, nerve regeneration, water deprivation, and so on, are a reflection of the fact that while a world war tends to check the progress of Physiology in most directions, it may accelerate it in others. By no means all of the new material has to do with war physiology, however, but is well distributed throughout the entire field. Despite some condensation in rewriting and the freer use of small type in the present volume, there has been a net increase of 30 pages in the text and an addition of approximately 1000 new references to the literature. As in past editions, the subject of the circulation is treated with especial thoroughness, and with a degree of authority possible only in the case of an author writing about a field in which he himself has made important original contributions.

M. J.

**CONTROL OF PAIN IN CHILDBIRTH.** By CLIFFORD B. LULL, M.D., F.A.C.S., Clinical Professor of Obstetrics, Jefferson Med. Coll.; Assistant Director, Phila. Lying-in Unit, Penna. Hospital, and ROBERT A. HINGSON, M.D., Surgeon, U. S. Public Health Service; Director, Post-graduate Medical Course, Phila. Lying-in Unit, Penna. Hospital. With an Introduction by NORRIS W. VAUX, M.D., Obstetrician-in-Chief, Phila. Lying-in Unit, Penna. Hospital. Pp. 356; 100 ills., 32 subjects in color. Philadelphia: Lippincott, 1944. Price, \$7.50.

ALTHOUGH this volume considers most of the drugs and techniques which are employed for the relief of pain during labor, it deals primarily with the continuous administration of local anesthesia *via* the caudal canal. Since Hingson is the outstanding proponent of this procedure, it is important to have him publish in full the results of his own experience. This is especially true, since many obstetricians are far from being convinced that this is a practical form of anesthesia that will stand the test of time. The book deals fully with the caudal technique, but its treatment of the other drugs and methods is such that it can hardly be considered a comprehensive work of general reference. There is also much to be desired in this volume from the standpoint of authorship. These weaknesses deal with such questions as the use of source material and references, organization of the data, style, English composition, simplicity in the selection of words, as well as the most efficient use of illustrations. It is impossible in the present space to consider these points in any detail, but they are mentioned in the hope that more attention be paid to these details in a future edition.

D. M.

**LARGE SCALE RORSCHACH TECHNIQUES.** A Manual for the Group Rorschach and Multiple Choice Test. By M. R. HARROWER-ERICKSON, ACAD. DIP., PH.D. Research Associate Department of Neuropsychiatry, University of Wisconsin, and M. E. STEINER, B.A., M.A., Personnel Section, General Electric Co., Bridgeport, Conn. Pp. 420; 70 ills., 47 tables. Springfield: Charles C Thomas, 1944. Price, \$8.50.

It is here assumed that the Rorschach (inkblot) worker has already mastered the specialized technique. For their group administration, these authors employ large scale Rorschach techniques, thereby vastly increasing the procedure's range value. A completely new test has been devised, termed the Multiple Choice Test, made available for the screening out of maladjusted individuals. The final chapters tell how the group method combined with the Multiple Choice Test enables the "psychologist, psychiatrist, educator, social worker or probation officer, *without any Rorschach training*, to profit by the experience of Rorschach and other subsequent workers." The volume includes a scoring key employed in this test. And here is also given for the first time, a statistical analysis of the 10 Rorschach cards.

After the class has assembled for this group method, in numerical order 1 slide of all the 10 cards is shown on a screen, and from each of them every individual being tested is to make 1 choice. Previously, the members of the

class had been supplied with a large record blank containing a list of 10 subjects from which 1 is to be chosen. As an illustration, the list for Rorschach card 1 reads: An army or navy emblem, Mud and dirt, A bat, Nothing at all, Two people, A pelvis, An X-ray picture, Pincers of a crab, A dirty mess, Part of my body, Something other than the above. Though an untrained person may administer the Multiple Choice Test, a well trained Rorschach worker will still be required to score and evaluate the group.

The Military Psychiatric Differentiation study was conducted by Lt. Floyd O. Due, (MC), USNR, Ens. M. Erick Wright, H-V (S), USNR, and Beatrice Wright, Ph.D. After 200 neuropsychiatric cases had been explored, it was concluded that the psychoneurotic sub-groups showed the most accurate inferences of maladjustment. Many organic and convulsive states could be differentiated from other groups. Response patterns often showed the presence of a psychopathic personality. Though many mental defectives produced very abnormal response records, they were not accurately discriminatory.

At the present writing, it appears that these authors have devised a new test that will reveal, with relative accuracy, the subject's personality, together with the degree of his maladjustment. Though the tedious Rorschach procedure had already attained a large sphere of usefulness, it is a real achievement to have contributed this short-cut method.

N. Y.

### NEW BOOKS

*Manual of Clinical Mycology.* Prepared Under the Auspices of the Division of Medical Sciences of the National Research Council by NORMAN F. CONANT, PH.D., DONALD STOVER MARTIN, M.D., DAVID TILLERSON SMITH, M.D., ROGER DENIO BAKER, M.D., and JASPER LAMAR CALLAWAY, M.D. Pp. 348; 148 figs. Philadelphia and London: W. B. Saunders, 1944. Price, \$3.50.

A CONCISE, correct and convenient presentation from the Duke University group of mycologists. This makes it authoritative. It is the kind of a book that has been long awaited by teachers, laboratory workers and practitioners.

F. W.

*Lead Poisoning.* By ABRAHAM CANTAROW, M.D., Associate Professor of Medicine, Jefferson Med. Coll.; Assistant Physician, Jefferson Hosp.; Biochemist, Jefferson Hosp., Philadelphia, Pa.; and MAX TRUMPER, PH.D., Lt. Commander, H-V(S), USNR, Naval Med. Research Institute, Bethesda, Md.; Formerly Lecturer in Toxicology, Jefferson Med. Coll.; Consultant in Industrial Toxicology, Cynwyd, Pa. To the Memory of HENRY LEFFMANN, Scientist, Scholar and Philosopher. Pp. 264. Baltimore: Williams & Wilkins, 1944. Price, \$3.00.

*Atlas of the Blood in Children.* By KENNETH D. BLACKFAN, M.D., Late Thomas Morgan Rotch Professor of Pediatrics, Harvard Med. School; Late Physician-in-Chief, Infants' and Children's Hosps., Boston; LOUIS K. DIAMOND, M.D., Assistant Professor of Pediatrics, Harvard Med. School; Visiting Physician and Hematologist, Infants' and Children's Hosps., Boston. With illustrations by C. MERRILL LEISTER, M.D., Associate Pediatrician, St. Luke's Hosp., Bethlehem, and Allentown General Hosp., Allentown, Pa. Pp. 320; 70 ills. in color. New York: Commonwealth Fund, 1944. Price, \$12.00. (Reviewed on p. 273.)

*Electrical Signs of Nervous Activity.* By JOSEPH ERLANGER, Professor of Physiology, Washington University, and HERBERT S. GASSER, Director, The Rockefeller Institute for Med. Research. Pp. 221; 113 figs. Philadelphia: Univ. of Penna. Press, 1937. Price, \$3.50.

*Endocrinology of Woman.* By E. C. HAMBLEN, B.S., M.D., F.A.C.S., Clinical Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke Univ. School of Med.; Chief of the Endocrine Division and Endocrinologist, Duke Hosp., Durham, N. C. Pp. 571; 157 figs. Springfield, Ill.: Charles C Thomas, 1945. Price, \$8.00.

- Medical Uses of Soap.* Edited by MORRIS FISHBEIN, M.D. With 10 Authors. Pp. 182; 41 figs. Philadelphia: J. B. Lippincott, 1945. Price, \$3.00.
- American Medical Practice in the Perspectives of a Century.* By BERNHARD J. STERN, PH.D., Lecturer in Sociology, Columbia Univ.; Visiting Professor of Sociology, Yale Univ. Pp. 156. New York: Commonwealth Fund, 1945. Price, \$1.50.
- Metastases. Medical and Surgical.* By MALFORD W. THEWLIS, M.D., Attending Specialist in General Medicine, U.S.P.H. Hosps., New York City; Attending Physician, South County Hosp., Wakefield, R. I.; Special Consultant, R. I. Dept. Public Health; Author, "Care of the Aged (Geriatrics)," Preclinical Medicine. Foreword by HUBERT A. ROYSTER, A.B., M.D., F.A.C.S., Honorary Chief Surgical Service, Rex Hosp.; Chief-of-Staff, St. Agnes Hosp.; Consulting Surgeon, Dix Hill State Hosp.; Fellow American Board of Surgery, Raleigh. Pp. 230; 13 ills. Charlotte, N. C.: Charlotte Medical Press, 1944. Price, \$5.00.
- The Story of a Hospital.* The Neurological Institute of New York, 1909-1938. By CHARLES A. ELSBERG, M.D., Chief of the Surgical Service (Emeritus), Neurological Institute, New York. Pp. 174; numerous ills. New York and London: Paul B. Hoeber, 1944. Price, \$3.50.
- Etiology, Diagnosis and Treatment of Amebiasis.* By CHARLES F. CRAIG, M.D., M.A. (Hon.), F.A.C.P., F.A.C.S., Colonel U.S.A., Retired, D.S.M.; Late Commandant, Army Med. School, and Assistant Commandant, Army Medical Center, Washington, D. C.; Emeritus Professor of Tropical Medicine, Med. School, Tulane Univ. of Louisiana, New Orleans, La. Pp. 332; 45 figs. Baltimore: Williams & Wilkins, 1944. Price, \$4.50.
- Familial Susceptibility to Tuberculosis.* Its Importance as a Public Health Problem. *Harvard University Monograph in Medicine and Public Health.* Number 5. By RUTH RICE PUFFER, DR.P.H., Tennessee Dept. of Health. Pp. 106; numerous figs. and tables. Cambridge, Mass.: Harvard Univ. Press, 1944. Price, \$2.00.
- Patients Have Families.* By HENRY B. RICHARDSON, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Cornell Univ. Med. Coll.; Attending Physician, New York Hosp.; Visiting Physician, Bellevue Hosp. Pp. 408. New York: Commonwealth Fund, 1945. Price, \$3.00.
- The Reticulo-endothelial System in Sulfonamide Activity.* By FRANK THOMAS MAHER, PH.D., Assistant Professor of Pharmacognosy and Pharmacology. Contribution from the Department of Pharmacology, Materia Medica, and Therapeutics in the College of Medicine. Pp. 232; numerous figs. and tables. Urbana, Ill.: Univ. of Ill. Press, 1944. Price, \$2.50.
- Ourselves Unborn.* An Embryologist's Essay on Man. By GEORGE W. CORNER. The Terry Lectures. Pp. 188; 18 figs. Conn.: Yale Univ. Press, 1944. Price, \$3.00.

## NEW EDITIONS

- The Woman Asks the Doctor.* By EMIL NOVAK, M.D., F.A.C.S., Honorary D.Sc. (Dublin), Associate in Gynecology, Johns Hopkins Med. School; Gynecologist, Bon Secours and St. Agnes Hosp. Illustrated by CARL CLARKE. Second Edition. Pp. 130. Baltimore: Williams & Wilkins, 1944. Price, \$1.50.
- Medical Diseases of War.* By SIR ARTHUR HURST, M.A., D.M., F.R.C.P., with the coöperation of H. W. BARBER, M.A., M.B., F.R.C.P.; H. B. F. DIXON, M.C., M.D., D.T.M. and H., F.R.C.P.; E. H. R. HARRIES, M.D., F.R.C.P., D.P.H.; F. A. KNOTT, M.D., F.R.C.P.; MELVILLE D. MACKENZIE, M.D., D.T.M. and H.; T. A. ROSS, M.D., F.R.C.P.; ARNOLD W. STOTT, M.A., F.R.C.P. Pp. 511; 48 figs. Baltimore: Williams & Wilkins, 1944. Price, \$6.00.

*Textbook of Medical Treatment.* By Various Authors. Edited by D. M. DUNLOP, B.A. (Oxon.), M.D., F.R.C.P. (Edin.), M.R.C.P. (Lond.); L. S. P. DAVIDSON, B.A. (Camb.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.); J. W. McNEE, D.S.O., D.Sc., M.D. (Glas.), F.R.C.P. (Edin.), F.R.C.P. (Lond.). With a Foreword by the late Professor A. J. CLARK, B.A. (Camb.), M.D., D.P.H., F.R.C.P. (Lond.), F.R.S. Third Edition. Pp. 1218; 26 figs. Baltimore: Williams & Wilkins, 1944. Price, \$8.00.

*The Avitaminoses.* The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, Ph.D., Emeritus Professor of Physiological Chemistry, Teachers Coll., Columbia Univ., and GILBERT DALLDORF, M.D., Pathologist of the Grasslands and Northern Westchester Hosps., Westchester County, N. Y. Third Edition. Pp. 438; numerous plates and tables. Baltimore: Williams & Wilkins, 1944. Price, \$4.50.

*The Pathology of Internal Diseases.* By WILLIAM BOYD, M.D., LL.D., M.R.C.P., Professor of Pathology and Bacteriology in the Univ. of Toronto, Toronto; Formerly Professor of Pathology in the Univ. of Manitoba, Winnipeg, Can. Fourth Edition. Pp. 857; 366 figs.; 8 colored plates. Philadelphia: Lea & Febiger, 1944. Price, \$10.00.

*Elements of Electrocardiographic Interpretation.* By LOUIS N. KATZ, A.M., M.D., Director of Cardiovascular Research, The Michael Reese Hosp., Chicago, Professorial Lecturer in Physiology, The Univ. of Chicago; and VICTOR JOHNSON, Ph.D., M.D., Professorial Lecturer in Physiology, The Univ. of Chicago. Third Edition. Pp. 44; 40 plates illustrating the more important deviations from the normal, selected from the files of the Michael Reese Hospital. Illinois: Univ. of Chicago Press, 1944. Price, \$1.00.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### SOME CLINICAL OBSERVATIONS ON AN OUTBREAK OF JAUNDICE FOLLOWING YELLOW FEVER VACCINATION\*

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AND

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THE nature and characteristics of the outbreak of jaundice that occurred in the Army during the Spring and Summer of 1942 has been concisely recorded in Circular Letters No. 45 S.G.O. dated May 13, 1942, and No. 95, S.G.O. dated August 31, 1942. It also received editorial comment in the *Journal of the American Medical Association*.<sup>4</sup>

Of what value then is a report of observations from a General Hospital overseas? Undoubtedly the most interesting and important question is that of etiology, and the nature of the icterogenic agent, a problem for the study of which only limited facilities were available at this hospital. The opportunity, however, of seeing a considerable number of similar cases of jaundice at the same time was unique in the experience of the medical officers concerned, and led to a somewhat different conception of the natural history of the disease, as well as to the recognition of certain symptoms which were unfamiliar. The data on the cases of jaundice observed in the 4th General Hospital is, therefore, recorded for comparison with and inclusion in similar data from other stations. It is apparently very similar to that recently reported from Brazil.<sup>8</sup>

The occurrence of epidemics of jaundice in armies is, of course, well known. Of the American Army, Blumer<sup>2</sup> goes so far as to say that with the possible exception of the Revolution, "whenever troops have been concentrated in this country the disease has usually appeared;" he records outbreaks in the War of 1812, Civil War, and Spanish War, as well as in World War I. In World War I it occurred on the

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Western Front<sup>6</sup> and was common at the Dardanelles.<sup>12</sup> In the present war there was a considerable number of cases among the Australian troops in the Middle East.

Between April 6 and September 30, 1942, 405 cases with jaundice were admitted to this hospital. By May 1, 20 cases had been admitted, and speculation was rife among the officers as to the nature of the epidemic. By the middle of May certain peculiarities in the distribution of cases had strongly suggested the possibility of association with certain lots of yellow fever vaccine. For instance, all of the 13 cases among the officers of the 4th General Hospital were from the group that had been on one transport where they received the vaccine from a single lot, while there were no cases among the enlisted men and officers who were on another transport and were vaccinated from a different lot. All the officers had been living in intimate contact both before embarking and after debarking the latter part of February. That jaundice had followed the use of certain yellow fever vaccines was also known from Findlay's reports.<sup>7</sup>

Of the 405 cases, the records of 398 were suitable for study. In 183 cases the date of yellow fever vaccination was known. The mean interval between vaccination and appearance of jaundice was 100.1 days; the shortest interval 66 days, and the longest 210 days. The median was 94 days. In only 28 (15%) of the cases was the interval greater than 120 days. These men were recorded as having been vaccinated from 16 different lots, but in only 4 was there a sufficient number to compare the interval between vaccinations and jaundice with different lots of vaccine. There was no significant difference. Seven patients gave a history of having had "catarrhal jaundice" from 6 months to 20 years previously. One patient stated that he had received yellow fever vaccine in October, 1939, before going to South America for an oil company and that he developed jaundice in January, 1940, together with a number of other employees of the same company. It was not possible to confirm these statements.

TABLE 1.—INCIDENCE OF PRESENTING COMPLAINTS IN 398 CASES

Jaundice . . . . .	273	Weakness . . . . .	28
Anorexia . . . . .	63	Vomiting . . . . .	23
Nausea . . . . .	63	Malaise . . . . .	6
Epigastric distress . . . . .	56	Hives . . . . .	2

The symptoms and mode of onset were almost indistinguishable from the "infectious hepatitis" described by Findlay,<sup>6</sup> Blumer,<sup>2</sup> Norton,<sup>13</sup> Pickles<sup>4</sup> and others. The onset was usually insidious, with anorexia, epigastric discomfort and dark urine. In many cases, however, the discoloration of skin and sclera was the first abnormality noted, and other symptoms did not develop for several days after icterus was apparent. The early appearance of dark urine is quite constant and usually noticed by the patient and is extremely valuable in early diagnosis. The more common presenting complaints are listed in Table 1—the total exceeding the number of patients for obvious reasons. The incidence of these and of certain other common symp-

toms is shown in Table 2. Urticaria occurred in only 10 patients, but was the presenting complaint in 2. The urticaria preceded the jaundice by 1 to 13 days, usually 7, and consisted of a few large wheals more commonly on the trunk than extremities. One patient developed urticaria after 22 days of jaundice.

TABLE 2.—INCIDENCE OF PRINCIPAL SYMPTOMS IN 398 CASES

	No.	%		No.	%
Jaundice . . . . .	398	100.0	Diarrhea . . . . .	46	11.5
Anorexia . . . . .	316	79.3	Malaise . . . . .	40	10.1
Nausea . . . . .	257	64.5	Fever . . . . .	64	16.1
Epigastric discomfort	185	46.2	Pyrosis . . . . .	60	15.1
Weakness . . . . .	202	50.7	Sleepiness . . . . .	21	5.3
Vomiting . . . . .	135	33.9	Upper resp. symptoms	35	8.7
Eructations . . . . .	108	27.1	R.U.Q. pain . . . . .	26	6.5
Headache . . . . .	79	19.8	Urticaria . . . . .	10	2.5
Constipation . . . . .	82	20.6			

It was difficult to obtain sufficiently accurate histories from many patients to determine the relation between the time of onset of symptoms and the appearance of jaundice. Ten patients gave a definite story of anorexia for between 2 and 4 weeks before the onset of jaundice, whereas 6 maintained that they had had epigastric or right upper quadrant pain for the same interval. An attempt to show the relation between the onset of symptoms and the appearance of jaundice is presented in Table 3. The apparent onset of symptoms and jaundice

TABLE 3.—RELATION OF ONSET OF SYMPTOMS TO APPEARANCE OF JAUNDICE

Days Before jaundice	Anorexia	Epigastric pain	Nausea	Dark urine	Any symp- toms at all
14 . . . . .	5	2	5	3	13
13 . . . . .	3	3	2	4	16
12 . . . . .	1	2	..	3	11
11 . . . . .	2	1	1	1	8
10 . . . . .	6	3	3	4	19
9 . . . . .	2	1	4	2	13
8 . . . . .	6	2	7	7	29
7 . . . . .	28	15	21	28	96
6 . . . . .	8	5	5	15	42
5 . . . . .	10	7	7	25	61
4 . . . . .	15	16	9	14	63
3 . . . . .	18	8	14	42	98
2 . . . . .	18	6	13	28	76
1 . . . . .	6	2	4	30	53
0 . . . . .	27	13	20	77	148
After jaundice					
1 . . . . .	2		1	4	
2 . . . . .	2	..	1	2	
3 . . . . .	1	2	2	2	
4 . . . . .	1	1			

at the same time is due to the large number of mild cases whose first knowledge that they were not well was when some friend told them that they were yellow. In the more typical and severer cases there were definite symptoms for a week before jaundice was detectable. The incidence of upper respiratory symptoms at the onset was considerably less than is usually encountered in epidemics of infectious hepatitis. Some 21 patients complained of unusual drowsiness and,

among these, this was a striking symptom. They slept almost continuously for several days, although could be aroused readily and when awake were completely clear.

The liver was recorded as palpably enlarged in 285 cases (71.6%). This is considerably higher than the figure of 20% given in Circular Letter No. 95. In 209 of these patients there was complaint of pain or tenderness on palpation of the liver, while in 76 instances the enlarged liver was not painful. Forty additional patients in whom the liver could not be felt complained of pain or tenderness in the right upper quadrant. The enlargement of the liver was usually only moderate, in only 21 cases was it recorded as being more than 5 cm. below the costal border. The spleen was palpable in 26 patients, and was usually not tender. A temperature above 99° F. during the period of hospitalization was recorded in only 68 (17%) of the cases. In 44 of these the maximum was below 100°, in 15 between 100° and 101°, and in 2, 104° F. The fever rarely lasted more than 2 or 3 days. A very few ran an irregular fever for a week to 10 days; a similar small group complained of frank chills. While on the wards a number of observers had commented on slow pulse rates, the bradycardia frequently associated with jaundice was not borne out by a study of the records. During the first 3 days of hospitalization only 1 patient had a mean resting heart rate below 50 per minute; in 13 it was between 50 and 60; in 98 between 60 and 70; and in 196 between 70 and 80. Seventy-nine had a mean resting heart rate between 80 and 90 per minute; 4 between 90 and 100, and only 1 over 100 beats per minute. This is a normal distribution.

Aside from the vague discomfort associated with the general feeling of malaise, severe joint or arthritic pains were distinctly uncommon, being recorded in only 2 instances.

In addition to the urticaria mentioned as one of the early symptoms, various skin eruptions occurred during the course of the disease. These included erythema, maculo-papular eruptions lasting a few days, usually over the trunk, petechia, purpura, and bleeding gums. Two patients had melena, 1 had an attack of erythema nodosum at the height of the jaundice. Two patients bled profusely enough to require transfusion, 1 from the bowel, and 1 from the gums. The tourniquet test was negative in all. Unfortunately at the time it was not possible to carry out prothrombin determinations.

One of the most striking phenomena, usually in the more severe and protracted cases, was the development of typical spider telangiectases, with a small central arteriole, pin-point pressure on which would cause the whole nevus to blanch. These occurred on the face, but were more common over the shoulders and pectoral regions. During recovery they completely disappeared and could not be seen or demonstrated, even when a particular lesion had been ringed for accurate localization.

Icteric indices were estimated on 337 patients. Usually one determination was made on admission, and subsequently at intervals if the jaundice seemed to be deepening. The mean of the maximum

icteric indices recorded for each of these patients was 64.4, the greatest number (55) being between 40 and 49. The distribution is shown in Table 4. Of the 16 patients with icteric indices over 150, 6 (37.5%) were over 30 years of age, while 22.3% of the whole group were over 30.

TABLE 4.—MAXIMUM ICTERIC INDEX

Icteric index	No. cases	Icteric index	No. cases
<10 . . . . .	1	80-89 . . . . .	15
10-19 . . . . .	19	90-100 . . . . .	13
20-29 . . . . .	38	100-109 . . . . .	13
30-39 . . . . .	45	110-119 . . . . .	11
40-49 . . . . .	55	120-129 . . . . .	14
50-59 . . . . .	29	130-139 . . . . .	7
60-69 . . . . .	32	140-149 . . . . .	5
70-79 . . . . .	28	>150 . . . . .	16

The difference is too slight to constitute evidence of a greater severity of the disease in the older group. In a small group icteric indices were determined at approximately weekly intervals. A chart of the results on 5 of these patients is shown in Figure 1. It is apparent that after

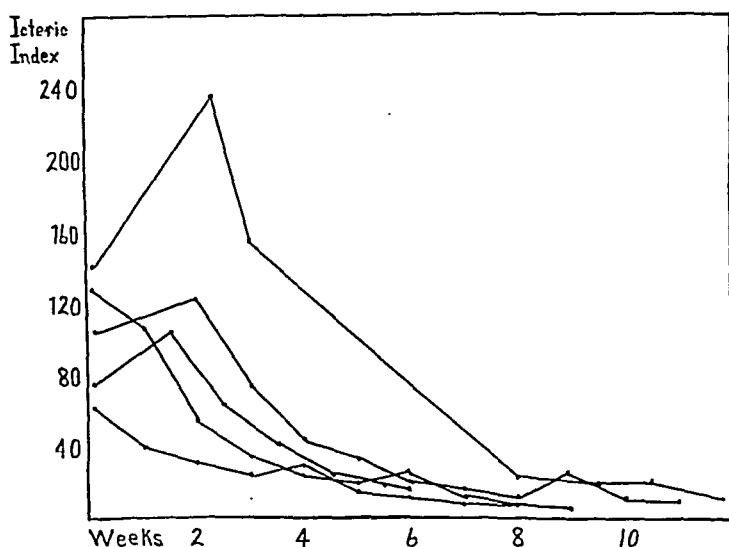


FIG. 1.—Rate of fall of icteric index.

convalescence begins, the chromogenic material in the serum diminishes at a more rapid rate during the first few weeks than it does later, although at this time the liver might be supposed to have recovered more fully. The reason for this is not clear. Attempts to estimate the icteric index from the color of the skin and conjunctiva during convalescence had a high error. It may be an expression of the relative amounts of bilirubin free in plasma and bound to plasma protein, or possibly some of the pigment is more firmly fixed in the tissues than the rest. It should be pointed out, however, that a similar type of curve of the elevation of bilirubin is obtained after its intravenous injection in normal individuals. After injection of sufficient bilirubin to raise the plasma concentration to 4 to 8 mg per 100 cc. (icteric

index 60 to 100), the blood level will have returned to normal in about 24 hours and none appears in the urine, the blood level falling along an exponential curve.

The urine was examined during the height of the disease in 329 patients. Sixty-one (18.5%) of these showed albumin; in 41 a trace, 15, 2+, and 4 a cloud. In all who recovered, the albumin disappeared before discharge. Abnormal numbers of cells or casts were not encountered. In no urine tested could a positive test for bile salts be obtained with either Hay's or Pettenkofer's test, although the specimens contained large amounts of pigment. In the severer cases there was a definite tendency for the specific gravity to be low, even when the volume was small, as in other types of so-called "bile nephrosis."

The onset of convalescence was not infrequently heralded by a profuse diuresis which persisted for several days and was not due to any significant increase in fluid intake. This aroused interest and speculation, but facilities were not available for study of its mechanism. It is recorded in the hope that it may be investigated when and where opportunities occur.

The infrequency of itching was a striking finding. Even the deeply jaundiced patient rarely complained of it, even on direct questioning. It was recorded as being present in only 13 patients. This, with the apparent absence of bile salts in the urine, invites speculation. Unfortunately, facilities were not available for estimation of the concentration of bile salts in the blood.

The mean leukocyte count in 194 examinations was 7620. There were only 15 counts above 10,000, the highest being 14,600, the lowest count was 4000. A careful differential count was made in 47 cases by an officer with special training in hematology (see Table 5). The commonly reported lymphocytosis in "catarrhal jaundice" was not found in these cases. The leukocyte count and differential must be regarded as within normal limits, and therefore, not of diagnostic value. Nor could any significant change in the smear be detected during the course of the disease.

TABLE 5.—DIFFERENTIAL LEUKOCYTE COUNT IN 47 CASES

	Average	Maximum	Minimum
Neutrophils . . . . .	58.2	79.0	32.0
Lymphocytes . . . . .	29.6	59.5	10.5
Young lymphocytes . . . . .	2.2	15.0	0.0
Mononuclears . . . . .	6.7	16.0	0.0
Eosinophils . . . . .	2.3	5.5	0.0
Basophils . . . . .	0.9	3.0	0.0

The mean sedimentation rate (Wintrobe method) in 215 cases was 11.6 mm. per hour. In only 39 was it above 15 mm. per hour. There was no relation between the intensity of jaundice and the more rapid sedimentation rates. The sedimentation rate was considered to be unaffected by this disease, the rapid rates observed being due to coincident upper respiratory infections.

The stools were rarely acholic, although an abnormally light color for a few days at the height of the disease was common. In only 85

cases, however, was this sufficiently noticeable to be recorded on the charts, and in only 10 cases are the stools recorded as "acholic" or "clay-colored." Unfortunately, at the time, the chemical tests were unreliable.

The cephalin-cholesterol flocculation test<sup>10</sup> was performed on 220 cases. On many of these it was repeated weekly until the test became negative. This test was selected in preference to other liver function tests for the following reasons: It is relatively easy to perform on large groups of patients; it is not invalidated by the presence of jaundice or disturbances in kidney function; and is primarily intended to show the presence of active parenchymal disease in the liver. Since one of the most important problems was to determine when a man should return to duty, this last feature was regarded as of importance. The technique was carried out exactly as originally described, but at first controls would be positive and all results had to be discarded. It was found out more or less by accident that it was first necessary for cephalin to "age" or oxidize for from 3 to 6 weeks. When solutions were made from the older cephalin, no more false positives occurred. We later found this had been noted by Rosenberg.<sup>15</sup> Opportunity to control the specificity of the test has been limited to 5 cases. These all showed negative reactions and were proved at operation to have obstructive jaundice, in 2 cases from stone and in 3 from carcinoma. The test is also positive in infectious mononucleosis as noted by Hanger, and it has recently been found to be positive during the acute phase of malarial fever. In all the early cases with acute symptoms the test was positive. In the average case the test would become negative in 3 to 4 weeks. This was usually by gradual change from 4+ to 2+ or down to negative, but a small group went from strongly positive to negative in a period of 1 week. It was quite usual for the test to become negative before signs of clinical jaundice disappeared. The converse was also true; a few cases were followed where jaundice had disappeared and the flocculation persisted. Most of these patients continued to complain of malaise and right upper quadrant pain on exertion. In 18 cases tests were done at weekly intervals for from 2 to 4½ months before the result was negative. These serial tests showed that, in spite of negative controls, the sensitivity of the reaction would occasionally vary from week to week. This was evident when three-quarters of the group would have a stronger reaction than the previous week, though their clinical condition was unchanged or improved.

From clinical observations it is felt that the flocculation test is of value in determining when the period of active liver damage is ended and in selecting those cases in which a prolonged period of convalescence is indicated.

Tests for urobilin in the urine were performed on 45 cases. Schlesinger's method was used and tests were repeated at intervals of 3 days. It was found that random single specimens were of little value, as false positives were frequent. This was corrected by using only samples from the total 24 hour urine volume. This intermittent excretion rate of urobilinogen in the urine has been fully described by Watson. It

was found that urobilinogen was usually absent from the urine during the acute phase with rising icterus, even when duodenal drainage showed some bile present in the intestinal tract.

During the early stage of recovery, tests for urobilin were very strongly positive, and then graded off to negative as the hyperbilirubinemia receded. The cephalin-cholesterol flocculation test became negative before urobilinogen disappeared from the urine on serial examinations. In 8 cases, urobilinuria cleared with recovery for from 7 to 14 days, then recurred and persisted for from 10 days to 2 weeks, without apparent change in the patient's condition. We have no explanation for this.

Duodenal intubation was carried out in 50 cases in all stages of the disease. In the first 20 cases the position of the tube was checked fluoroscopically; thereafter when a free flow of bile-stained fluid was not obtained. A sample (A) was collected, and then 50 cc. of warm 25% magnesium sulfate introduced. Ten minutes later a second specimen (B) of 50 to 75 cc. was taken and separated from a third (C) specimen. Microscopic examination was done on the B and C specimens. Free HCl was present in the stomach of all but 2 cases, a normal finding. Bile was always present in the duodenal contents, even when the jaundice was severe and mounting. However, the specimens were usually cloudy and very viscid, even allowing for contamination by gastric contents. Stimulation by magnesium sulfate in no case caused a flow of dark brown gall bladder bile. This was true even in cases where the patient had recovered clinically and jaundice had nearly cleared. Apparently the gall bladder is in a state of stasis for several weeks, even in mild cases.

On direct microscopic examination of the centrifuged duodenal sediment of the B and C specimens, some of the cases showed a moderate to marked cellular exudate. Many of these cells appeared to be neutrophilic leukocytes. Better to determine their nature, the duodenal contents were directly aspirated into formalin and fairly satisfactory hematoxylin and eosin stains prepared. It was then seen that the cells, apparently leukocytes, were in reality mononuclear cells with fragmented nuclei. The cells appeared definitely abnormal, the most striking change being the fragmentation, pyknosis and karyorrhexis of the nuclei. In addition, vacuoles in the cytoplasm were frequently noted. It was thought that these cells were associated with the disease in the liver. Slides were made from 17 cases of hepatitis and 10 with no evidence of liver disease. In 7 of the 17 cases of hepatitis, and in 3 of the control series, the abnormal cells previously described were found. In reviewing the experiences of others in duodenal intubation, it was found that Fidler, Innes and Davidson<sup>5</sup> had presented good evidence that these cells were due to the local irritation of the magnesium sulfate. The cells they found following its use were identical with ours, and they, too, at first identified them as leukocytes. It seems important to emphasize that, in studying the cellular content of duodenal and biliary secretions, concentrated magnesium sulfate should not be used as a stimulant.

Attempts were made to isolate a possible etiologic agent with the material available. These were uniformly negative, and are recorded merely as a matter of record. Duodenal contents from 5 patients were collected shortly after jaundice developed, pooled, filtered through Elford membrane with a pore diameter of 600  $\mu$ m. The sterile filtrate was inoculated subcutaneously into a *Macacus cynomolgus*. The monkey did not show any symptoms nor become jaundiced during the succeeding 5 months, nor was the serum collected at intervals icteric. Serum from a single early case was injected subcutaneously into another monkey with negative results. Filtered sterile duodenal contents were also inoculated onto the chorioallantois and into the amnion of 12-day chick embryos. The livers of embryos inoculated by the latter method showed some changes, but these were just as marked in controls inoculated with duodenal content from normal individuals.

Because of the uncertainty of the nature of the jaundice when it first appeared, the question arose in the minds of some medical officers whether it was due to leptospiral infection. Agglutination tests were, therefore, performed with the serum of 25 typical cases, using five strains of leptospira, *L. icterohæmorrhagica*, *Australianis A and B*, *pomona*, and *mitis*. All were completely negative.

The prolonged action of morphine and of the barbiturates in these patients was very striking. A dose of  $1\frac{1}{2}$  to 3 gr. of amytal or  $1\frac{1}{2}$  gr. of sodium pentobarbital frequently would cause extreme drowsiness for 24 to 48 hours. The use of any barbiturates was, therefore, abandoned, and morphine used only when absolutely necessary and then in half the dose that would have been used for a non-jaundiced patient. No definite abnormal reactions to codeine were observed. This drug controlled the restlessness of severe cases satisfactorily without significant depression of respiration.

Because of the common exhibition of magnesium sulfate in "catarrhal jaundice" and its alleged action as a cholagogue, it was given to a group of 21 patients in 15-gm. doses each morning before breakfast. Another group of 21 patients, admitted on the same day to the same ward, served as control. All were treated alike in other respects. No difference in the two groups could be detected in symptoms, rate of clearing of jaundice, or decrease in the size of the liver.

The majority of the patients who could eat were given a low fat-high carbohydrate diet containing approximately 450 gm. carbohydrate, 80 gm. protein and 45 gm. fat. Those with little anorexia were allowed the regular hospital diet. The rationale of fat restriction rests on reasonably firm evidence. The merit of restricting protein is less sure. The work of Whipple, Ravdin, and others would suggest that a high protein intake should afford the greatest protection to the liver from the noxious agent. Some patients, however, refused to eat meat, while others apparently experienced no discomfort from it. Of 81 patients questioned particularly about their ability to eat meat since the onset of their jaundice, 61 (75%) had eaten it regularly with no discomfort or aversion, whereas 25% had been unable to do so. Nor



was there any difference in their appetite for different meats. The return of appetite usually followed a characteristic pattern. The patient would be hungry for breakfast, which he would eat avidly and without discomfort. Lunch was less appealing, and might be followed by mild epigastric discomfort, while supper was repulsive, and what little was eaten was apt to be followed by epigastric discomfort, cramps, nausea, and at times, vomiting. This could not be wholly attributed to the character of the foods served at the different meals, for it occurred also in patients on special diets receiving the same foods at all meals. These patients are unable to eat much at one time. Frequently an adequate caloric intake can be maintained and nausea avoided by giving small quantities of food at 2-hour intervals, similar to the routine used in an active peptic ulcer.

While the advantage of high carbohydrate diets in the milder cases is problematical, the value of glucose in the severer cases seemed very definite from clinical observation. Glucose (200 gm. intravenously as a 10% solution in the course of 24 hours) not infrequently transformed a miserable, nauseated, vomiting patient into one in reasonable comfort and able to take food by mouth. Physiologic salt solution alone did not have this effect. In patients with severe anorexia and nausea, the administration of 200 to 300 gm. glucose daily in fruit juice seemed to be of definite value in shortening the period of discomfort. Unfortunately this rests only on clinical impression, as controlled groups were not attempted. In 2 cases of coma the improvement after intravenous glucose was striking. It seemed that 200 gm. daily was about the minimum from which any benefit appeared. While this exhibition of glucose certainly was followed by symptomatic improvement, this does not constitute evidence that it had any direct effect on the hepatitis.

The severer cases received thiamin hydrochloride, thiamin hydrochloride and nicotinic acid, or polyvitamin tablets empirically. There was no evidence apparent of any particular benefit. Atropine, extract of belladonna, and magnesium oxide appeared to give relief in some patients with epigastric discomfort, but not consistently. A few patients with low plasma proteins, and 2 with severe anemia the result of hemorrhage, received blood transfusions.

With the marked anorexia, weight loss was rapid at the beginning of the disease. This was usually about 10 pounds; in the severer cases from 20 to 30. While return of appetite and gain in weight usually coincided, this was not always so. In such patients gain in weight afforded the better indication of progress.

While in the milder cases convalescence was quite rapid, in the severer ones it was prolonged. Frequently there would be complaint of right upper quadrant pain or "heavy feeling" particularly on exertion for several weeks after the jaundice had disappeared. Symptomatic cure was more closely correlated with a negative flocculation test than with disappearance of jaundice. The average period of hospitalization was 29.5 days. One hundred and twelve patients remained 1 to 2 months, while 25 were in hospital more than 2 months.

No late sequelæ have been observed in this hospital. Four of these protracted cases deserve brief mention.

**Case Histories.** CASE 1. E. C., 22 year old white male, received yellow fever vaccine March 15, 1942, developed nausea, vomiting and dark urine on May 20, and jaundice 4 days later. The liver was enlarged 3 cm. below the costal margin, he became deeply jaundiced, but appeared to be making the usual satisfactory recovery during the first weeks of July, with definite clearing of his jaundice. On July 23, edema of the face was noted, definite ascites about August 1, and he was admitted to the 4th General Hospital on August 7, 2½ months after the onset of his illness. He was in considerable respiratory distress due to the marked ascites. There was also marked edema of the face and legs, the liver was small to percussion, the blood pressure was 126/80. He was seriously but not critically ill and perfectly rational.

*Laboratory Reports* at this time showed the following: Urinalysis—faint trace of albumin and bile. R.B.C. 3,830,000; Hb. 65%; differential—normal; icteric index 53; blood urea nitrogen 11 mg. %. Plasma proteins total 5.68 gm. %, plasma cholesterol 175 mg. %; bleeding and clotting time normal. Abdominal paracentesis was done on the 2d day; 2,000 cc. of bile-stained clear fluid was removed, specific gravity 1.014. Following this his condition rapidly deteriorated, and in 24 hours he was in complete coma, with incontinence of urine and feces, and marked fruity odor to the breath.

He was treated with intravenous glucose, saline, blood plasma and large doses of thiamin chloride and nicotinic acid. After 4 days in coma his condition improved and within a week he was rational and taking food by mouth. The abdominal paracentesis incision continued to drain profusely until about August 22, when it sealed over. No demonstrable ascites was present at this time and patient's condition was good. Within a week, moderate ascites recurred. At this time plasma proteins showed total 5.02 mg. %, albumin fraction 1.51; globulin 3.51; A/G ratio 0.4. He was given 1500 cc. of plasma in a period of 5 days and maintained a diuresis of 3000 to 4000 cc. for 1 week, and in 10 days was edema-free. This marked diuresis was unaccompanied by any significant rise in plasma albumin value, the A/G ratio not returning to a normal figure until 3 months later. The cephalin cholesterol test first taken on August 10 remained positive until October 15. Hippuric acid excretion test was 3.46 gm. in 4 hours on November 10. He was sent back to full duty on November 26, 1942, 6 months after the onset of his illness.

This case is reported in detail because it shows apparent good recovery following severe alteration of liver function, with coma lasting nearly a week. At no time was there evidence of disturbed kidney function and the level of icterus was always moderate.

CASE 2. W. R., sergeant, aged 53, developed anorexia and abdominal distress on July 7, 1942. On July 17, icterus was first noted and shortly thereafter ascites. He was admitted to the 4th General Hospital on July 26, 1942. At this time he was deeply jaundiced, icteric index 185, and showed marked ascites with some edema of the legs. The liver was 6 cm. below the costal margin and tender. The heart and blood pressure were normal. Urinalysis and blood counts were normal; plasma proteins total 6.6 gm. with a normal A/G ratio. Cephalin flocculation test gradually decreased from 4+ on July 27 to 1+ on September 30. The ascites gradually disappeared during the month after admission, but he continued to have digestive symptoms and failed to gain strength. He was evacuated to the United States.

This case developed ascites within 3 weeks of the onset of his disease, in the presence of normal plasma proteins. It seemed probable that portal obstruction was the major factor in production of the ascites.

CASE 3. E. B., corporal, aged 28, developed generalized urticaria followed by anorexia, nausea and vomiting, about June 1, 1942. Jaundice appeared 2 weeks later and he was admitted to the hospital. He made an uneventful recovery and was discharged to duty July 22. Though he did not appear icteric, icteric index on day before discharge was reported as 23.

He was readmitted to the 4th General Hospital on October 2, 1942. He had failed to gain weight and strength and had been noticed to be jaundiced on occasions. He had also developed dyspepsia and pain in the right upper quadrant. At this time gastro-intestinal and gall bladder Roentgen rays were negative. He continued to be weak, failed to gain weight, and icteric index varied between 16 and 30. Cephalin flocculation test was 2+, hippuric acid excretion 2.7 gm. in 4 hours. On January 7, it was recommended that he be returned to the United States. His illness at that time had persisted 7 months.

CASE 4. J. N., private, aged 20, developed crampy abdominal pain, anorexia and jaundice about June 1, 1942. His past history revealed he had had jaundice for 6 weeks in 1938, 1 month in 1939, and again in 1940. During his course in this hospital extensive laboratory procedures failed to find any cause for recurring jaundice. He failed to gain weight and strength, dyspepsia continued, and icteric index remained about 20. On January 8 he was recommended for return to the United States 7 months after the onset of symptoms.

These 2 cases, from their duration alone, can be classed as subacute or chronic hepatitis. There is, however, no real ground for believing that they may not eventually recover. Chronic fatigue, failure to gain weight, and continued dyspepsia, were the prominent clinical features of both, as they were in a number of other protracted cases. Also a noteworthy feature was the behavior of the icteric index, which dropped in the usual time to a level of about 20, but then failed to return to the normal base level.

There were 2 deaths in this series of 405 patients, a mortality of 0.49%. While the pathologic changes undoubtedly are primarily the concern of the Army Institute of Pathology, they are appropriately considered here also. The first (Case 5) demonstrates the gradual development of liver insufficiency and the value, albeit temporary in this instance, of glucose. The second (Case 6) was one of rapidly developing liver insufficiency in a man who, although probably jaundiced, had been on duty until some 48 hours before death. Fortunately no cases of sudden death during convalescence, similar to those recorded by Martin,<sup>12</sup> were encountered. One man, however, symptom-free, and with no apparent jaundice, who undertook to walk up several flights of stairs without permission, developed dyspnea, tachycardia and substernal pain which persisted for 24 hours.

CASE 5. W. A. G., aged 21, was admitted June 22, 1942, complaining of abdominal pain. The date of yellow fever vaccination and lot number were not available. He had anorexia and nausea since about June 1, and vomited on one occasion while in the field. Jaundice appeared about June 12, and he was admitted to another Army hospital. On admission here his temperature was 98.2° F., pulse 60, respiration 18. He was cooperative, mentally clear, and did not appear in any acute distress. The skin and sclera were deeply jaundiced. Blood pressure was 90/70. The liver was palpable 2 cm. below the costal margin and was tender. The remainder of the physical examination was normal. His urine had a specific gravity of 1.020, contained 2+ albumin, no sugar, casts or abnormal sediment. Icteric index was 110, sedimentation rate 6 mm. per hour. He seemed to be progressing satisfactorily for a week. Then his jaundice became much deeper, he completely lost his appetite, and com-

plained of severe abdominal cramps, constipation, weakness and vomiting. He became very somnolent, confused, and finally impossible to arouse. The liver was no longer palpable. Urine sp. gr. 1.015, trace of albumin, no sugar, bile pigments but no bile salts. Hb. was 90%, R.B.C. 5.8 million, and W.B.C. 9000 (65% neutrophils, 30% lymphocytes), icteric index 245, blood non-protein nitrogen 38 mg. per 100 cc. Spinal fluid was faintly but definitely icteric, contained 26 mg. protein and 19 cells (7 neutrophils, 12 lymphocytes) per 100 cc. The Ross Jones test for globulin was negative. He was given 300 gm. dextrose, 50 mg. thiamin hydrochloride and 100 mg. nicotinic acid with 4000 cc. fluid intravenously daily for the next 5 days. He showed considerable improvement. He became conscious and was able to take fluid and food by mouth. On July 16, blood non-protein nitrogen was 33, urea nitrogen 11, sugar 102 mg. per 100 cc. Plasma proteins were reduced to 4.95 gm. per 100 cc. Plasma CO<sub>2</sub> combining power was 63 vol. per 100 cc. The urine continued to show albumin. The white count had risen to 18,000 with 80% neutrophils. There was no anemia. Bleeding time 3 minutes, clotting time (tube method) 17 minutes 25 seconds. Patient continued to be fairly alert mentally and to take sufficient fluid and carbohydrates by mouth, so that infusions were discontinued. He developed marked abdominal distention and some ascites. Abdominal paracentesis was performed on July 22, removing 1600 cc. He was given 500 cc. plasma intravenously on July 21 and again the next day. At this time he was taking 300 gm. carbohydrate and 90 gm. protein daily. By July 27, he had again become delirious and irrational and intravenous glucose, fluid and thiamin hydrochloride were resumed. He showed some purpuric spots but no gross hemorrhage. He lapsed into deeper coma. On August 2, temperature and pulse rate began to rise and he died August 3, with a final temperature of 105° F., pulse 150. Shortly before death blood non-protein nitrogen was 38, urea nitrogen 17, and sugar 100 mg. per 100 cc.; CO<sub>2</sub> combining power 62 vol. per 100 cc. and plasma proteins 4.9 gm. per 100 cc., icteric index 166. Urine volume was in excess of 700 cc., specific gravity 1.009 and it contained a trace of albumin but no sugar.

At AUTOPSY all tissues and organs were deeply jaundiced. There was 2000 cc. bile-stained fluid in the peritoneum. The liver weighed 960 gm. It was firm, nodular, and the edges were thin and sharp. The capsule was thin and the surface reddish yellow, with numerous large and small nodular areas which were yellowish green. It cut with considerably increased resistance. The normal pattern was replaced by large bulging nodules which were yellowish green and raised above the surrounding liver tissue. Between these nodules of regenerating and necrotic tissue there were flat, reddish brown zones in which the normal architecture was preserved. The bile ducts presented a normal appearance. The kidneys weighed 200 gm. each, with a smooth dark red and yellow surface. The cut surfaces were moist, bulging, and the cortex was considerably increased, measuring 12 mm. in width. The differentiation from medulla was indistinct. There was confluent bronchopneumonia in the lower lobes of both lungs. The stomach, small and large intestines, showed moderate edema of the mucosa with occasional small areas of hyperemia and a few petechiæ. The other organs presented no significant gross abnormality. There were multiple varices in the mesentery, mesocolon and posterior peritoneum, but not elsewhere.

MICROSCOPIC EXAMINATION.—The liver showed an extremely variegated appearance. The large nodules were regenerated tissue in which the architecture was fairly well preserved. The liver cells were arranged in cords, were large, and showed numerous mitoses and multinucleated forms. The periportal tissue was increased in some areas and showed proliferation of bile ducts, but no pseudo-lobule formation. In other areas there was extensive necrosis, principally central, but also involving the peripheral zones of the lobules extensively. The necrotic liver cells had been replaced by fibroblasts and well-vascularized young connective tissue. Other areas showed degenerative changes in the liver cells, swelling, vacuolization and pigmentation. None of the cells showed focal hyaline necrosis, and there was only an occasional

ochre cell. A conspicuous change was plugging of bile ducts and canaliculi with large masses of bile pigment, at times with infiltration of neutrophils and lymphocytes. Many cells in regenerated areas were stained with bile pigment. Sections stained with Sudan IV showed only small amounts of fat, principally around the central veins in regenerated areas.

The normal architecture of the *kidneys* was preserved. The glomeruli were normal. The tubules were the seat of marked disease, focal in character, involving principally the ascending limb of Henle and the distal convoluted tubules. These contained large pigmented casts, often mixed with neutrophils, leukocytes, lymphocytes and degenerated epithelial cells. The tubular epithelium was denuded in many places, in others replaced by flattened cells. The interstitial tissue, especially in the pyramids, was slightly edematous with sparse infiltration of lymphocytes in some areas. Fat stains showed marked fatty degeneration of the proximal tubules.

CASE 6. W. G. B., aged 23, was admitted July 15, 1942, in coma and moderately jaundiced. The only history obtainable was that he had been left in quarters the day before, when his company went on a hike. That evening he was found to be difficult to arouse and was admitted to the station hospital, where he was described as comatose, restless, and entirely uncoöperative. Except for jaundice, the physical examination was normal, the blood pressure 140/80. His urine contained no sugar or acetone. During the night his coma became deeper and he was transferred to this hospital by ambulance the next morning. On admission he was entirely unresponsive, showed periodic respirations, deep jaundice, and a few coarse râles at the base of each lung. Blood pressure was 105/60 and pulse regular at 140 per minute. The liver and spleen were not palpable. Deep reflexes were hyperactive with bilateral sustained ankle clonus. Urine had a specific gravity of 1.018, contained a trace of albumin, no sugar, and a few coarsely granular casts. Hb. 85%, R.B.C. 4.6 million, W.B.C. 12,900 per cmm. (84% neutrophils, 14% lymphocytes, 1% each monocytes and basophils). Non-protein nitrogen was 36 and urea nitrogen 7 mg. per 100 cc. Plasma proteins 6 gm. per 100 cc. Icteric index 140. The spinal fluid was faintly yellow, contained 2 cells per cmm. and 20 mg. protein per 100 cc. He was given 10% glucose intravenously, thiamin hydrochloride and, with the onset of pulmonary edema, intravenous digitalis. He died 9 hours after admission, following several convulsions.

At AUTOPSY all the organs and tissues were deeply bile-stained. There was no free fluid in thorax or abdomen. There were numerous ecchymoses beneath the endocardium of the interventricular system. The *lungs* were deep red, firm and contained considerable frothy bloody fluid. The *liver* weighed 1055 gm. The surface was uneven with slightly raised bright yellow areas. On section, the normal architecture was preserved in some areas, while in others there were irregular areas of coagulation necrosis, yellowish gray in color. The *extrahepatic bile ducts* were normal. The *kidneys* weighed 195 gm. each. On section, the division between cortex and medulla was somewhat indistinct. The pyramids were deep red. There was no edema of the *gastro-intestinal tract*.

MICROSCOPIC EXAMINATIONS. The *liver* showed various appearances. Those from the yellowish necrotic areas showed extensive necrosis with complete wiping out of the normal architecture, so that an amorphous granular material alone remained. In other sections the normal architecture could be distinguished, but was much altered. There was extensive necrosis, more marked about the central veins. Most of the necrotic cells were pale pink staining, but some showed bright red hyaline necrosis and resembled Councilman bodies, while others were ochre yellow and resembled the cells described by Villela.<sup>16</sup> Neither of these changes was very conspicuous, but when searched for were easily found. The intact cells showed some fatty metamorphosis and vacuolization of the cytoplasm, but there were no cytoplasmic or nuclear inclusions. There were moderate numbers of binucleated cells and mitoses. The kidney architecture was preserved and the glomeruli appeared normal. There was marked swelling with vacuolization and granularity of the cytoplasm in the cells of the proximal convoluted tubules. Many of the lumina were closed by swelling of the epithelium.

Both cases thus showed extensive necrosis and atrophy of the liver with varying degrees of fibrosis and regeneration. The necrosis was principally central, although not strikingly so. Both cases showed minimal hyaline necrosis, although occasional Councilman bodies were present. In 1 case there were numerous ochre bodies such as have been described by Villela in cases of yellow fever, where death was delayed, and which, therefore, cannot be regarded as characteristic of that disease. The liver lesion seems indistinguishable from that of "infectious hepatitis" where no yellow fever vaccine had been administered. The changes in the kidneys of the first case seem identical with those seen after transfusion reactions, crush injuries<sup>3</sup> and in deep jaundice<sup>1</sup> (the "lower nephron syndrome").

After an interval of 4 months with only an occasional admission for "jaundice," another epidemic of over 100 cases was encountered among troops returning from the combat zone, who had yellow fever vaccine from 12 to 18 months previously. This group appeared to have a disease indistinguishable from the epidemic jaundice or infectious hepatitis described among civilians and in armies in previous wars. While the spontaneous disease and that following vaccination are extremely similar, certain differences have been noted. The incubation period of the natural disease is usually given as about 30 days. While it was impossible to determine this among the troops, evidence is afforded by 2 cases in the Army Nurse Corps. One nurse had taken special care of the 1 fatal case 19 days before she developed jaundice, while the other had been "out" with an officer who developed jaundice 2 days later. She became jaundiced after 28 days. The average incubation period in the postvaccination cases, on the other hand, averaged about 3 months, corresponding with that described by Findlay in postvaccination jaundice. Fever and upper respiratory symptoms were more frequent in the naturally occurring disease. Forty-eight per cent had fever (above 99° F.) compared with 17% in the postvaccination group. If the usual mode of spread is by droplet infection, this may account for the latter observation. No definite second wave of jaundice was encountered in the postvaccination group; this may also be due to the fact that the noxious agent was introduced by an abnormal route, and that concentration of the hypothetical virus did not occur in the upper respiratory tract. In general, lassitude and malaise were more marked in the natural disease, the onset more abrupt, and convalescence more rapid. Thus the average interval between onset of symptoms and jaundice was 3.1 days, while in the postvaccination disease it was 7.2 days. The average period of hospitalization was only 18.2 days for the natural epidemic, and 29.5 days for the postvaccination cases.

**Summary.** Clinical observations on 398 cases of jaundice following yellow fever vaccination are recorded. In 183 cases where date of vaccination and jaundice was accurately known, the mean interval was 100.1 days. The symptoms are indistinguishable from those of infectious hepatitis, but the onset more insidious. The mean interval between onset of symptoms and jaundice was 7.2 days. Fever occurred

in only 17%, albuminuria in 18.5%. Leukocyte count, differential count, and sedimentation rates were normal. The mean maximum icteric index was 64.4. The cephalin flocculation test was positive in the 220 cases in which it was performed, and furnished a valuable index of progress. Bile was present in the duodenum of 50 cases intubated at all stages of the disease. There is no evidence that biliary obstruction is a factor in production of the jaundice. The value of dietary treatment in the milder cases is problematical, but the value of glucose in severe cases was quite evident. There were 2 deaths, a mortality of 0.49%. The average period of hospitalization was 29.5 days. Convalescence was prolonged.

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### ANAEROBIC SEPTICEMIA

#### REPORT OF 6 CASES WITH CLINICAL, BACTERIOLOGIC AND PATHOLOGIC STUDIES

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SEPTICEMIAS due to anaerobic, non-sporeforming bacilli occur in only a small proportion of all cases of systemic infection seen by the clinician. However, the high death rate in such infections warrants that considerable attention be given them in order that an early diagnosis be made and suitable treatment if possible be instituted. In a review of 144 cases of septicemia seen at the Mayo Clinic, Rosenow

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and Brown<sup>11</sup> found that the causative agent in 6 of them was *Bacteroides funduliformis*, and that the fatality rate was 100%. A report by Herrell and Brown<sup>8</sup> on the treatment of septicemic infections before and after the advent of the sulfonamides gives 265 cases, 8 of which were caused by members of the genus *Bacteroides*. The fatality rate here was also 100%. Observations as to the highly serious nature of *Bacteroides* septicemias have also been reported by Thompson and Beaver,<sup>13</sup> Dixon and Deuterman<sup>5</sup> and Lemierre.<sup>9</sup>

It is apparent from the above-mentioned reports that no completely satisfactory method of treatment for these infections has been devised. Since thrombophlebitis at the site of the initial lesion is a characteristic finding, ligation of the veins, if accessible, below this area has been suggested as a procedure of possible value as a means of limiting the spread of the infection. Although the sulfonamides have not been particularly effective against anaerobic infections, the successful treatment of a case of *Bacteroides* septicemia by the use of sulfonamides has been reported by Brown, Williams, and Herrell.<sup>3</sup> They recorded the recovery of the patient by maintaining a high sulfapyridine blood level (14 mg. to 19 mg.), plus multiple blood transfusions. Anderson,<sup>1</sup> using similar therapeutic procedures, noted the recovery of a child with a *Bacteroides funduliformis* septicemia. Both of these cases were treated with sulfonamide compounds from the date of admission to the hospital, and before bacteriologic studies had been made. Goodnough<sup>7</sup> reported the recovery of a patient with a liver abscess from which *B. funduliformis* was isolated. Treatment consisted of incision and drainage of the abscess plus chemotherapy with the sulfonamides. He believed that the sulfonamides contributed to the patient's recovery. It was not determined in this case whether a blood stream infection existed.

In considering the value of the sulfonamides in septicemias due to *Bacteroides*, the experimental work of Prevot<sup>10</sup> is of interest. Prevot produced septicemias in rabbits by intravenous inoculation of a suspension of *Spherophorus funduliformis* (*Bacteroides funduliformis*). Treatment of these infected rabbits with repeated subcutaneous injections of sulfanilamide resulted in a 76% recovery rate. The disease was invariably fatal in the untreated controls. He concluded that sulfonamide therapy was of definite value if given early, in large doses, and continued until danger of relapse had disappeared.

Since apparent successful therapy of these infections has followed early administration of the sulfonamides, an early diagnosis may be of paramount importance. This can best be made by careful observation of characteristic clinical symptoms and use of satisfactory bacteriologic procedures. For this reason, we are reporting the findings in 6 cases of septicemia due to *Bacteroides* that we have seen, together with the bacteriologic techniques that have been found satisfactory by us for isolating these organisms.

**Case Reports.** CASE 1. H. J., a white female, age 20 years, was admitted to the Memorial Hospital on November 3, 1936, complaining of a right-sided headache, double and failing vision. In June, she had developed a sore throat



which was followed by a peritonsillar abscess that ruptured spontaneously into the mouth. This series of events was followed by fever and chills at irregular intervals for several weeks, after which she felt quite well again. In August, she developed a throbbing type of headache associated with spasmodic vomiting spells, which continued throughout the course of the illness. Her vision became less acute than formerly, and at times a double vision was noticed.

A general physical examination was negative. Neurologic examination revealed the following positive findings; bilateral choking of the optic disks; left lower facial weakness; greatly diminished abdominal reflexes on the left and an equivocal Babinski on this side. There was no jaundice or clinical evidence of lung pathology.

On November 6, a well encapsulated abscess in the parietal region was aspirated and about 40 cc. of thick green pus removed. A culture of this pus on anaerobic media showed a growth of *Bacteroides gonidiaformans*. The patient failed to respond to treatment and died on November 24, 1936.

*Autopsy Findings.* Autopsy, performed 2 hours after death, was limited to the head. The brain showed an area of bulging 5 cm. in diameter in the right occipito-parietal region in which the convolutions were flattened, the meninges dull, and the subarachnoid space contained turbid exudate. On section of the brain after fixation there was a well walled-off abscess 5 cm. in diameter in the right occipital lobe, which extended from the level of the splenium of the corpus callosum almost to the tip of the occipital lobe. The right cerebral hemisphere was markedly swollen and the right lateral ventricle almost obliterated. Microscopic sections from the abscess wall showed organizing granulation tissue containing many newly formed capillaries. The abscess cavity contained a polymorphonuclear exudate. The white matter adjoining the abscess wall showed edema and marked perivascular accumulations of small round and plasma cells.

CASE 2. J. B., a colored male, age 22 years, was admitted to the St. Philip Hospital on July 8, 1937, complaining of fever, chills, night sweats, sore throat and pain in the right chest. He had been expectorating about  $\frac{1}{2}$  cup of thick purulent sputum a day. The patient had developed a sore throat on June 25, and had been put to bed by his family physician 2 days later. The above-mentioned symptoms developed rapidly after this time. His past history was entirely negative except for the fact that, in 1934, he had been successfully operated on for a stab wound of the heart at the St. Philip Hospital.

On initial examination, the temperature was 102.8° F., respirations 42 per minute, pulse 112, and blood pressure 144/62. The essential findings consisted of a yellowish discoloration of the sclerae; enlarged, cryptic, and inflamed tonsils; moist râles in both lung bases with bronchial breathing present posteriorly over the lower one-third of each lung, and a liver edge that was felt 2 cm. below the costal margin.

The urine showed a trace of albumin and was positive for bile. The routine blood studies showed no significant findings except for a leukocytosis of 11,850. The non-protein nitrogen was 41, and the icteric index 96.4.

The patient presented a characteristic picture of septicemia. Repeated aerobic blood cultures, however, proved to be negative and the patient died on July 18, 1937, 10 days after admission, with a diagnosis of septicemia, cause undetermined.

*Autopsy* (3 hours and 20 minutes after death). There was a small abscess in the right peritonsillar region. The veins draining this region were distended and filled with pus as far as their junction with the right internal jugular vein, which in turn was filled with a partly organized thrombus extending downward into the right innominate vein. At its lower extent, the wall of the internal jugular vein was thinned and soft, but showed no perforation. In the soft tissue above the right sterno-clavicular joint, there was an abscess which extended caudally for 2 cm. in the tissue overlying the carotid sheath.

Both lungs were increased in weight (left, 580 gm.; right, 340 gm). Both showed irregular yellowish pink areas with a dark red border raised above

the pleural surface. On section, many of these nodules were coalescent and showed central areas of softening. The larger pulmonary veins contained thrombotic material. Microscopic sections showed typical septic infarcts of the lung and thrombophlebitis of the branches of the pulmonary vein.

The spleen (640 gm.) was very soft. The pulp had the color and consistency of thick red paint and scraped away easily. Microscopically, there was marked congestion of the pulp and sinuses with a greatly increased number of neutrophils in the pulp.

Microscopically, liver and kidneys showed interstitial accumulations of neutrophils, lymphocytes and macrophages with interstitial edema.

Anatomic diagnosis: Peritonsillar abscess, right. Thrombophlebitis of right internal jugular vein and its tributaries, right innominate vein, and pulmonary vein. Septic infarcts of lungs. Acute splenic tumor. Acute interstitial hepatitis. Acute interstitial nephritis. Jaundice.

Although positive bacteriologic findings are lacking on this case, the clinical picture is typical of a *Bacteroides* septicemia, as described by Sodeman<sup>12</sup> in an excellent résumé of anaerobic septicemias published at this time. Since this case illustrates well the problems involved in making a diagnosis, it is included here.

CASE 3. J. K., a colored male, age 24 years, was admitted to the St. Philip Hospital on March 23, 1938, complaining of a sore throat, swollen neck and headache. He had had several chills followed by high fever and diffuse sweats.

On initial examination the temperature was 103° F., respirations 24 per minute, pulse 95, and blood pressure 110/60. The skin and mucous membranes were jaundiced. The tonsillar region and pharynx could not be examined because of trismus. The neck was absolutely rigid to anterior, posterior and lateral motion. Extending downward from the angle of the right mandible and disappearing beneath the clavicle were 2 firm, tender, cordlike structures. Coarse rhonchi were heard over the chest. The liver and spleen could not be palpated.

The urine showed a heavy trace of albumin and the presence of hyaline casts. The blood count was not significant, although there was a leukocytosis of 25,000. The blood chemistry showed a non-protein nitrogen of 113 mg., and an icteric index of 134. The Wassermann and Kline tests were positive. There were 1670 W.B.C. in the spinal fluid, with 96% neutrophils. A portable Roentgen ray of the chest showed irregular mottling extending from both hilar regions. A blood culture taken on March 25 was subsequently positive for *Bacteroides gonidiaformans*.

The patient was given 6 gm. of sulfanilamide in normal saline by hypodermoclysis on March 24, and 10 gm. by the same method on March 25. In addition, glucose and saline were given intravenously as general supportive treatment. None of these therapeutic measures seemed to influence the course of the disease, and the patient died on March 25, 1938, 3 days after entering the hospital. Permission for autopsy was refused.

CASE 4. L. A., a white female, age 20 years, was admitted to the Medical College Hospital on April 21, 1941. Three weeks prior to her admission she had a tonsillitis which had developed into a peritonsillar abscess. Two weeks before entering the hospital she had chills with high fever and a swelling of the right side of the face. Her right eye had become swollen shortly after this. Because of the fact that she had failed to respond to treatment with sulfathiazole, she was referred to the hospital.

On admission, her temperature was 103° F., respirations 24 per minute, pulse 120, and blood pressure 124/80. The right eyelid was swollen and closed, and the right pupil was widely dilated. The fundus was normal. The tonsils were moderately injected, but no purulent exudate was noted. No pathologic findings were noted in the chest, heart or abdomen.

The urine was negative. Examination of the blood showed a slight hypochromic anemia. There was no leukocytosis. The icteric index and non-protein nitrogen were normal.

One week after admission, she developed a septic arthritis of the left shoulder,

and 25 cc. of thick, green pus was aspirated, from which was grown *Bacteroides funduliformis*. Blood cultures taken on April 28 and 30 were also positive for this organism. On May 2, there was Roentgen ray evidence of multiple infarction in the lung. Three days later, she was explored for a brain abscess with negative results.

Treatment, in addition to general supportive measures and repeated blood transfusions, consisted of chemotherapeutic measures. Oral administration of sulfathiazole was started on April 21, and 3 days later a blood level of 3.2 mg. per 100 cc. was obtained. Since there appeared to be no improvement in her clinical state, the drug was discontinued and, on April 28, treatment begun with sulfapyridine. On April 29 and 30, the oral dose of sulfapyridine was supplemented with sodium sulfapyridine given intravenously. The blood levels were recorded as being 15.4 mg. and 17.3 mg., per 100 cc. on April 29 and 30, respectively. Neither of these drugs influenced the course of the disease and the patient died May 8, 1941.

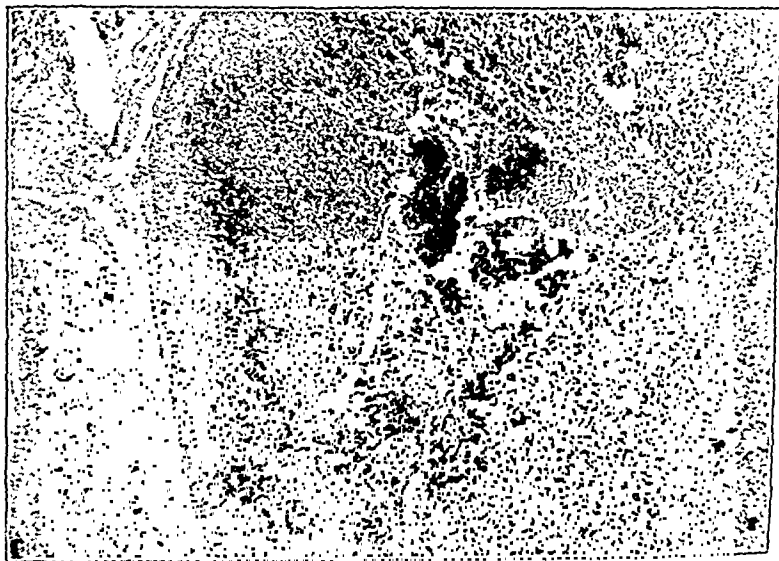


FIG. 1.—Section of lung showing at the left, the wall of a branch of the pulmonary vein with a small tributary. The vein lumen is filled with a thrombus containing many neutrophils. On the right the wall of the vein is completely destroyed and the lumen is continuous with an abscess in the lung parenchyma showing an area of softening. (Hematoxylin and eosin,  $\times 90$ .)

*Autopsy* (2 hours postmortem). There was an open 6 cm. wound of the left shoulder anteriorly with a small amount of thick purulent yellow drainage. Both lungs contained well-defined nodular areas of consolidation. On section some of these areas showed soft necrotic or frankly purulent central areas. The visceral pleura immediately overlying these areas was covered with fibrin. Microscopically, many of the branches of the pulmonary vessels were filled with thrombi, some of them undergoing organization. Areas of hemorrhage into the alveoli with necrosis of the alveolar walls, characteristic of infarction, were present. Some of these showed accumulations of neutrophils with necrosis and liquefaction. (See Fig. 1.)

Spleen weight, 210 gm. On section the cut surfaces bulged and the pulp scraped away easily. Microscopic sections showed congestion of the pulp by R.B.C. and a markedly increased number of neutrophils. No abscesses were present.

The entire base of the brain was covered by a thick yellow purulent exudate lying in the subarachnoid and subdural spaces and extending posteriorly over

the tentorium cerebelli and involving most of the cranial nerve roots. The cerebellum showed no gross changes.

The pituitary was increased to three times its normal size. The pituitary fossa was increased in size and covered by purulent exudate. The sphenoid and ethmoid sinuses contained purulent material.

Microscopic sections of the brain showed a fibrinopurulent meningitis with early necrosis of the exudate. The walls of the meningeal vessels were infiltrated by neutrophils. Within the white matter there was moderate perivascular infiltration of neutrophils. Sections of the pituitary showed fibrinopurulent exudate surrounding the gland and small focal areas of necrosis just beneath the capsule.

Anatomic diagnosis: Fibrinopurulent basal meningitis, more marked on right. Purulent sinusitis of ethmoid and sphenoid sinuses. Osteomyelitis of pituitary fossa. Multiple bilateral embolic pulmonary abscesses. Thrombophlebitis of pulmonary veins. Draining subcutaneous abscess of left shoulder region. Acute splenic tumor.

At autopsy, *Bacteroides funduliformis* was isolated from the spinal fluid and *Bacteroides funduliformis* and *Staphylococcus aureus* were isolated from a brain abscess and from the lung.

CASE 5. L. P., a colored male, aged 41, was admitted to the St. Philip Hospital on August 24, 1941, complaining of pain and swelling in the right knee and left elbow. The joint pains had begun about 3 weeks prior to this date and had affected both knees, wrists, and elbows. This general involvement had gradually subsided and the pain became localized in the right knee and left elbow. For 1 week, he had noted progressive swelling of these joints. Throughout the period of this illness, he had been troubled with an extremely sore throat. Ten days before entering the hospital he had expectorated a mouthful of thick pus.

On initial examination, the temperature was 102.8° F., respirations 24 per minute, pulse 120, and blood pressure 125/75. The patient was well developed and well preserved, rational and alert. The mucous membrane of the throat was extremely hyperemic and somewhat edematous. Several small superficial ulcers were present on both tonsils. The chest, lungs and heart were normal. There were no masses, palpable organs or areas of tenderness in the abdomen. The left elbow and right knee were swollen, tender, hot and painful to touch and passive motion.

The urine was negative. The routine blood studies showed a moderate hypochromic anemia and a leukocytosis of 13,750. The Wassermann and Kline tests were positive.

The clinical course was characterized by a constant temperature elevation varying from 99° to 104° F. until September 3, when it became normal and remained so until his discharge. This was associated with a tachycardia of from 90 to 120 per minute without arrhythmia. There were no chills or profuse sweats. On August 24, the right knee was aspirated with the removal of 15 cc. of thick foul pus which had an odor resembling rancid butter. A culture of this fluid was reported positive for *Bacteroides funduliformis*. Two days later the left elbow was aspirated and pus of a similar nature removed. A similar organism was isolated from this fluid. At this time, it was noted that the left side of the neck was beginning to swell and that the area involved was hot and tender. On August 28, a Roentgen ray examination was made of the cervical vertebrae. The report indicated the presence of a small swelling at the level of the 5th and 6th vertebrae which was thought to be a retropharyngeal abscess. Blood cultures were consistently negative, but an agglutination test using the patient's serum against the organism isolated from the knee was positive in a 1 to 80 dilution. On September 3 a large, left cervical abscess was incised and drained with the evacuation of a large quantity of thick pus. Bacteriologic studies on this showed the presence of *Bacteroides funduliformis*.

Treatment consisted of general supportive measures as regards food and fluid. Sulfathiazole was given daily from August 24 to September 4. Blood levels of 2.6 mg. and 7 mg. per 100 cc. were obtained on September 1 and 3,

respectively. After this time, the medication was changed to a saturated solution of potassium iodide. This was discontinued on September 16, 1941.

The patient's hospital course was uneventful thereafter, and he was discharged on October 20, 1941, apparently well.

CASE 6. H. L., an acutely ill, white, male, age 23 months, was admitted to the Medical College Hospital on October 4, 1941. A few weeks prior to this date he had developed a diarrhea associated with persistent vomiting. These symptoms had lasted for 1 week. Following this he developed a sore throat and the anterior cervical lymph nodes became markedly swollen and tender. On September 27, 1941, the child began to have a hard shaking chill daily and this continued until the day of admission.

On initial examination, the temperature was 102.8° F., respirations 36 per minute, pulse 136. The skin was hot and dry, but clear. There was a small hemangioma over the left temporal area. The anterior, cervical lymph nodes were found to be slightly enlarged, but not tender. The chest, lungs and heart were negative. The abdomen, extremities, and neuromuscular apparatus were normal upon examination.

Routine examination of the urine was negative. The blood showed a persistent and severe hypochromic anemia (hemoglobin 50%, R.B.C. 3,320,000) and leukocytosis of 26,000. Routine aerobic blood cultures were negative.

After hospitalization, the clinical course was characterized by the daily occurrence of hard, shaking chills with profuse sweats. These were associated with temperature elevations varying between 104° and 107° F. On October 4, an anaerobic blood culture was reported positive for *Bacteroides funduliformis*. This finding was confirmed by a second blood culture on October 15. There was little change in the general clinical behavior until October 13, when many coarse râles were heard in both lung fields. Roentgen ray studies made on October 15 revealed an extensive irregular mottling of the lung fields suggesting bronchopneumonia.

Treatment consisted of general supportive measures in regard to diet and liquid. In addition, 3 blood transfusions of 250 cc. each of citrated blood were given. Sulfadiazine was used intensively from the time of admission in relatively large doses until October 17, when the blood level was found to be 20.1 mg., at which time numerous crystals were found in the urine.

On October 18, the temperature suddenly returned to a normal level and thereafter remained normal. The patient was discharged from the hospital on November 1, 1941, apparently completely cured.

**Bacteriological Studies.** The species of organisms responsible for these anaerobic septicemias are members of the genus *Bacteroides*. They are found, as mentioned by Dack,<sup>4</sup> "as normal inhabitants of the mucous membranes of the body, inhabiting the upper respiratory tract, the colon and the genital tract." Infection occurs after damage to the mucous membranes, which allows the organism to gain a foothold in the tissues. Certain other conditions are probably essential in order that infection may take place, since most of these species appear to have a low degree of invasiveness. Lemierre has mentioned that a thrombophlebitis is a common finding at the site of the initial invasion, and possibly the stasis of blood brought about as the result of this establishes conditions which are suitable for the multiplication of these anaerobes.

The organisms may be cultivated either from the blood or from the metastatic abscesses which occur. Such cultivation depends upon the use of a media enriched with body fluids and suitable anaerobic conditions. We have found that many of the non-sporeforming anaerobes will grow well in veal infusion, 0.3% semisolid agar, containing 0.5%

sodium citrate and 0.3% dextrose. This media is put into 125-cc. Erlenmeyer flasks in 60-cc. amounts and is used routinely in our laboratories for blood culture work. The blood of the patient in this case taking the place of the body fluid needed for enrichment of the media.

Growth of *Bacteroides* occurs at the bottom of the flask, and may first appear within 2 to 4 days, depending upon the number of organisms in the initial inoculum. Morphologically, they are gram-negative, non-sporeforming bacilli with a great tendency to pleomorphism and irregularity in staining. They appear in culture as very short and/or filamentous rods. In pus from abscesses, the short forms predominate. The latter forms appear bipolar when stained by Gram's method. The long forms show irregular stained areas, at times giving a beaded appearance to the organism. *Bacteroides gonidiaformans*, the organism isolated from 2 of the cases differs in morphology from *Bacteroides funduliformis* in that, as stated by Bergey,<sup>2</sup> "gonidia form within the rods, developing into short or long wavy filaments." The characteristic morphology of these organisms as described above, together with their anaerobic growth requirements, is sufficient to warrant a preliminary bacteriologic diagnosis while further cultural and pathogenicity studies are being carried out.

Surface colonies can be obtained later by using any of the well known methods for anaerobic cultivation of bacteria and are best obtained when fresh blood agar slants are used. The colonies are small, convex and greyish in color. When inoculated into chopped meat tubes, there is a slight gas formation with the development of a foul odor, but no apparent digestion of the meat. Acid and slight gas production occurs in dextrose. Lactose and saccharose are not fermented. Gelatin is not liquefied and no growth occurs in litmus milk.

Intraperitoneal inoculation of saline suspensions of cultures of *Bacteroides funduliformis* into guinea pigs resulted in the production of a purulent, fibrinous peritonitis with death of the animals usually within 48 to 72 hours. Localized abscesses developed when the organisms were inoculated subcutaneously into mice. Usually the abscesses healed spontaneously.

It is of interest to note that agglutinins appear in the blood of infected individuals. Blood serum for serologic tests was obtained from 2 of the patients. On the 4th day after admission, a blood agglutinin titer of 1 to 80 was obtained on Case 4, using the organism isolated from the patient as an antigen. One week later the titer had risen to 1 to 320, and was still at that level 2 weeks later, the last time that blood was obtained. A blood specimen from Case 5 obtained 3 days after admission, gave an agglutinin titer of 1 to 320 against the homologous organism. Cross-agglutination studies with these 2 strains indicated that they were antigenically similar. Agglutination studies were not carried out on the other patients. Both of the above-mentioned cases recovered. Case 4 had been treated with sulfathiazole and potassium iodide, and Case 5 with sulfadiazine and multiple blood trans-

fusions. Whether the appearance of antibodies may have played a part in the recovery is not known.

**Comment.** Septicemias due to organisms of the genus *Bacteroides* arise from inflammatory or suppurative lesions in the tissues or body cavities where the organisms live under physiologic conditions. Here they grow and multiply, invade the regional veins and produce a thrombophlebitis, frequently giving rise to septic emboli which are borne to distant areas. The sites from which these organisms are most apt to invade the blood stream are the tonsils and peritonsillar regions, the middle ear and mastoid, teeth and gums, the appendix, the uterus and pelvic organs, and the prostate. Of these, peritonsillar abscesses are by far the most frequent source of infection.

Probably the most characteristic finding in this type of lesion is the thrombophlebitis which occurs in the veins draining the area of supuration. The work of Fraenkel<sup>6</sup> in Germany, in 1926, pointed out the universal occurrence of this type of lesion which, at times, was limited to the peritonsillar veins, but often extended out to invade the external and internal jugulars. Thrombophlebitis offers a valuable clinical sign in anaërobic infections of the structures of the head and throat, particularly since suppuration is often not clinically visible, as in the cases of *deep peritonsillar abscesses*. When the original site of infection lies in the prostate, appendix or uterus, the clinical value of this pathologic condition disappears. Not only is the thrombophlebitis a valuable physical sign, but it is also the characteristic pathologic lesion, and offers the basis on which this type of septicemia differs in part from the septicemias usually encountered in aërobic infections.

Infected emboli are dislodged from the main thrombus, and are disseminated through the body. The first organs involved are naturally the lungs. Multiple septic infarcts soon break down into multiple abscesses, producing such symptoms as dyspnea, expectoration, chest pain and cough, and such physical signs as coarse, moist râles, and scattered areas of consolidation. Occasionally empyema results. From these areas in the lungs, secondary, infected, emboli arise to be carried to diverse areas in the body, the most frequent sites of lodgment being: (1) The liver; where the lesion may be a single or multiple abscess or a diffuse hepatitis as in Case 2. Clinically, as in our case, jaundice of a severe nature may result. (2) The joints; the patient may complain of severe generalized joint pains without presenting objective findings. In other cases, massive suppurative lesions of the joint may occur. (3) The kidney; embolic nephritis with albuminuria, casts, W.B.C. and reduced renal function may result. (4) The brain; an embolic encephalitis results which often localizes with the formation of a brain abscess, as in our Case 4.

The general reaction of the patient is characterized by fever, chills, and profuse sweats, with wide variation in temperature readings over a 24-hour period.

In treatment, general supportive measures, such as fluids orally and parenterally, and repeated blood transfusions, are essentially necessary. The ligation of the neck veins below the area of thrombo-

phlebitis is of possible value. Necessarily, this procedure can be adopted only when the veins are accessible and when metastatic lesions have not been established. The early use of high blood levels of the sulfonamides, together with multiple blood transfusions may be of value in these infections. Encouraging results have been reported in 2 cases<sup>1,3</sup> in which this therapeutic procedure has been instituted, but we have also recorded 1 case in which sulfathiazole and sulfapyridine plus blood transfusions were used, which terminated fatally. This case was further complicated by a *Staph. aureus* septicemia, which may have influenced the outcome. One other case in our group, which was treated with sulfanilamide alone, terminated fatally. The efficacy of this mode of treatment will depend upon the results obtained after further trial.

The successful and early laboratory diagnosis of these infections depends to a large extent upon the information given to the bacteriologist by the clinician. Anaerobic cultures should be suggested in cases of suspected septicemias which have clinical symptoms similar to those mentioned above, and where aerobic cultures are consistently negative. Obviously a simple media suitable for the growth of both aerobes and anaerobes would be of distinct value to the bacteriologist. We have suggested such a media, which, while we make no claims as to originality, has been used satisfactorily by us for the cultivation of anaerobes of the genus *Bacteroides* from the blood.

The morphologic characteristics and the anaerobic nature of these organisms, as seen in the initial culture, is often sufficiently striking to warrant a tentative bacteriologic diagnosis of *Bacteroides* septicemia. Therapeutic measures may then be instituted while further biochemical and agglutinative studies on the organism are being performed.

Agglutinins are formed during the course of the infection and might serve as a means of diagnosis where there has been failure to isolate the specific organism. We have been able to demonstrate such antibodies in the 2 cases from which blood was obtained for this purpose. Since both of these cases recovered, it is interesting to speculate upon the possibility of the part they had in the recovery of the patients. However, we did not obtain blood serum for agglutination from the other cases which terminated fatally.

**Conclusions.** The non-sporeforming, anaerobic bacilli of the genus *Bacteroides* invade the blood from certain focal areas in the body where these organisms live habitually.

The most characteristic pathologic symptom is a thrombophlebitis of the regional veins, which occurs in all cases. From this source, the infection is disseminated throughout the body by means of septic emboli.

The detection of such infections depends upon the careful observation of certain characteristic symptoms and the use of suitable cultural technique for the isolation of the organisms.

Agglutinins appear in the blood stream of infected patients, and may serve as a means of diagnosis where there is failure to isolate the organism.



Early treatment by means of high levels of the sulfonamides together with multiple blood transfusions appears to offer possibilities as a successful mode of therapy in these highly fatal septicemias and is worthy of further trial.

Since this paper was written two additional reports have appeared on *Bacteroides* infections treated with sulfonamides. These cases are described elsewhere.<sup>14, 15</sup>

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### THE COINCIDENCE OF ALLERGIC DISEASE, UNEXPLAINED FATIGUE, AND LYMPHADENOPATHY; POSSIBLE DIAGNOSTIC CONFUSION WITH INFECTIOUS MONONUCLEOSIS\*

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A GROUP of cases with uncontrolled clinical allergic manifestations whose major complaint was fatigue was recently studied by one of us (T.G.R.) in conjunction with Elizabeth Barber Gibson.<sup>5</sup> The fatigue or weakness in these individuals was unrelieved by what is ordinarily considered an adequate amount of rest. Rowe<sup>7,8</sup> recognized this complaint as an expression of the allergic reaction, giving it the descriptive term of "allergic toxemia." Our observations agreed with those of Rowe in that this symptom occurred most commonly in association with some other allergic manifestation, more frequently in women than in men, and usually the result of allergic intolerance to foods. Significant numbers of atypical mononuclear cells were observed in the peripheral blood of many of these cases. These cells, identical with the atypical lymphocytes observed in infectious mononucleosis and best described by Downey,<sup>2</sup> comprised as high as 25% of the

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differential count. Although such cells were distinctly less in number than is commonly seen in the acute stage of infectious mononucleosis, the blood findings in the allergic individuals were compatible with the subsiding phase of glandular fever.

Infectious mononucleosis was often suspected in patients with allergic disease because of the complaint of fatigue, the finding of atypical lymphocytes in the differential counts, and the not infrequent past history or physical finding of tender, swollen cervical glands. Confusion in the differential diagnosis of allergic disease and infectious mononucleosis was further heightened by the common age incidence of the two manifestations. Both occur in young adults otherwise in the best of health and at an age, generally speaking, when the individual's immune response is most vigorous. Repeatedly negative heterophil antibody determinations had been found in several of these cases prior to their coming to our attention for an allergic study. Negative titers were again obtained at the time of their allergic investigation.

Independently, one of us (R.A.H.) had noted the presence of atypical mononuclear cells in the differential white cell counts of approximately one-fifth of the Freshman nursing class of 75 in the course of routine blood examinations. These cells also had the characteristics of the atypical lymphocytes observed in infectious mononucleosis. Upon the basis of this finding alone, several were suspected of having infectious mononucleosis, but heterophil antibody determinations were negative, with the exception of 1 case. This individual, subject to bronchial asthma and allergic rhinitis, was found to have a positive titer in a dilution of 1/2048; she also had the clinical features of infectious mononucleosis including extreme fatigue and a generalized lymphadenopathy. At the time she had a total leukocyte count of 17,100 and a differential count of 18% polymorphonuclear leukocytes, 69% large lymphocytes, of which practically all were atypical forms, 7% small lymphocytes, and 6% monocytes. Her blood was followed at monthly intervals and the number of the atypical lymphocytes slowly returned to normal.

The opinion was expressed that several of the other cases having atypical mononuclear cells at the time of their examination may have been in the recovery or residual phase of infectious mononucleosis, or that an epidemic of that disease had been present in the nurses' dormitory. This did not seem probable, since similar blood variations had been noted in the survey of the incoming class the preceding year.

As a consequence to these independent observations in groups of allergic and "normal" individuals, we recorded an allergy history, and repeated the blood counts in the same group of nurses a year after their earlier examinations. Each member of the 2 upper classes in the Nursing School was studied, a total of 140 cases. In addition, the individual hospital records were reviewed to determine whether the diagnosis of infectious mononucleosis had ever been suspected. Each matriculating student nurse had been subjected to a complete physical examination, and about 5% of them had been rejected because of some

physical disability. The group of student nurses had remained under very close medical supervision, since they were required to report to the Medical Clinic in the event of even minor illnesses.

In obtaining the allergy history, each person was asked whether she had been subject to periods of fatigue, unrelieved by the customary amount of rest. This admittedly was a difficult question; the answer depended in large part upon the amount of work performed and the amount of sleep obtained. However, under the carefully regulated conditions of nursing training the amount of work was approximately the same for each individual, and each person was required to live in a dormitory where strict rules regarding the time of reporting for duty and retiring were enforced. Under these circumstances, reasonably reliable answers to this question might be expected.

Each individual was asked whether she had had tender, swollen cervical glands, and if so whether this had occurred with or without accompanying upper respiratory infections. The nurses were also asked whether or not they had ever been suspected of having infectious mononucleosis or glandular fever. It might be added that this query was regarded humorously by the group as it had been a common experience to have been suspected of this disease. In response to this question, many answered: "Not yet!"

Eighty-three, or 59.2%, of the group of 140 had a definite past history of allergic disease. The remaining 40.8% were negative. The criteria used for judging a positive allergy history were those used by Vaughan<sup>5</sup> in determining the incidence of allergic manifestations in a sample population.

In the positive group of 83 cases, infantile or flexural dermatitis had occurred in 10 cases, asthma in 16, pollinosis or seasonal hay fever in 31, the probable diagnosis of perennial allergic rhinitis was made in an additional 30 cases. Of the latter group, it should be said that it is difficult to determine the presence or absence of an allergic rhinitis from the history alone; in these cases, particularly when seen at the time of nasal symptoms, the appearance of the nasal mucous membranes and the examination of the nasal secretions for eosinophils aided in making the diagnosis. A non-seasonal allergic rhinitis as judged by the history existed as the sole allergic manifestation in only 10 of the 30 cases; in the remainder one or more other allergic expressions had existed at some time in the past. Cases were encountered which obviously needed to be followed for months before a correct appraisal as to the presence or absence of an allergic rhinitis could be made. This type of follow-up was not attempted in this series. Doubtful cases were not included in the positive group.

Urticaria on repeated occasions or in prolonged attacks occurred in 27 individuals. A history of recurrent sick headaches was present in 22. Definite gastro-intestinal allergic symptoms occurred in 15. This diagnosis was suspected in several others, but in retrospect could not be substantiated and was not used as a criterion for placing a given case in the positive series. Frequent, recurrent canker sores occurred in 21 of the 83 positive cases, and in 9 of 57 with negative

histories. Five nurses of the positive group gave histories of serum sickness. No such cases were found in the negative group. The occurrence of either canker sores or serum sickness was not regarded as evidence for labeling a person an allergic individual. As might be expected, the majority of those in the positive group, 60 of 83 cases, had more than one allergic manifestation in their past history.

In response to the question: "Do you have periods of fatigue unrelieved by rest?", 43 (51.8%) of the positive group answered in the affirmative against 3 (5.3%) of the negative cases.

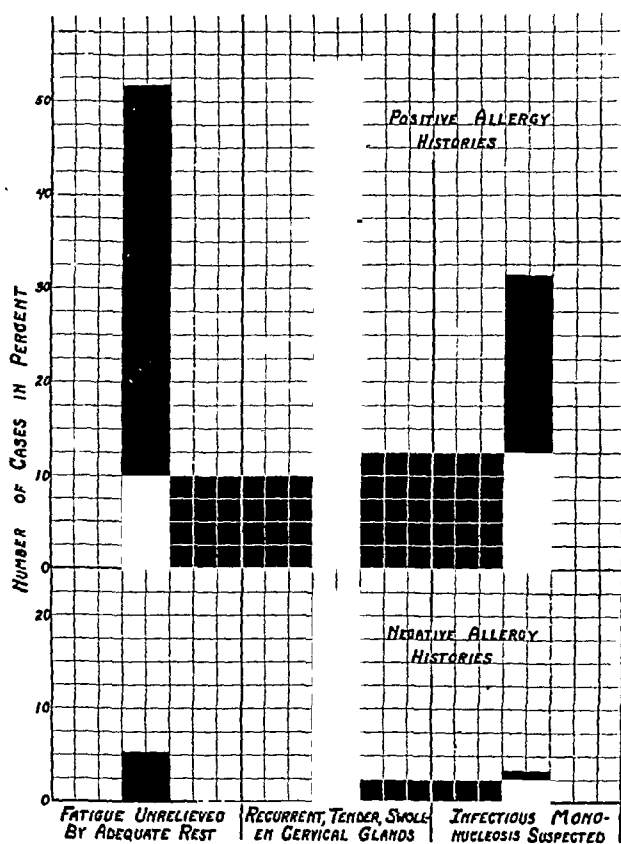


FIG. 1.—Symptoms of unexplained fatigue, recurrent, tender, swollen cervical glands and the suspicion of infectious mononucleosis in relation to a history of allergic disease.

A past history of recurrent, tender swollen cervical glands was obtained in 44 (54.2%) of the positive group and in 13 (22.8%) of the negative cases. Within the positive series noticeable cervical gland involvement occurred only in association with upper respiratory infections in 12, both in association with and in the absence of upper respiratory infections in 17, and spontaneously or without reference to upper respiratory infections in 15. Of the cases with negative histories for allergy, 8 fell into the first group, 1 in the second, and 4 in the third. Of the latter 4, where cervical gland involvement had occurred, without relation to an upper respiratory infection, 1 case was diagnosed

as infectious mononucleosis, 1 noted swollen glands with each menstrual period, and 1 had noticed tender enlarged cervical glands intermittently since a preceding mastoid infection. (See Fig. 1.)

The majority of the individuals answering this question in the affirmative had been subject to repeated bouts of swollen glands, often dating back to childhood. The terms upper respiratory infection and the common cold were used synonymously. The characteristic features of this clinical entity were described in each case as the question was asked.

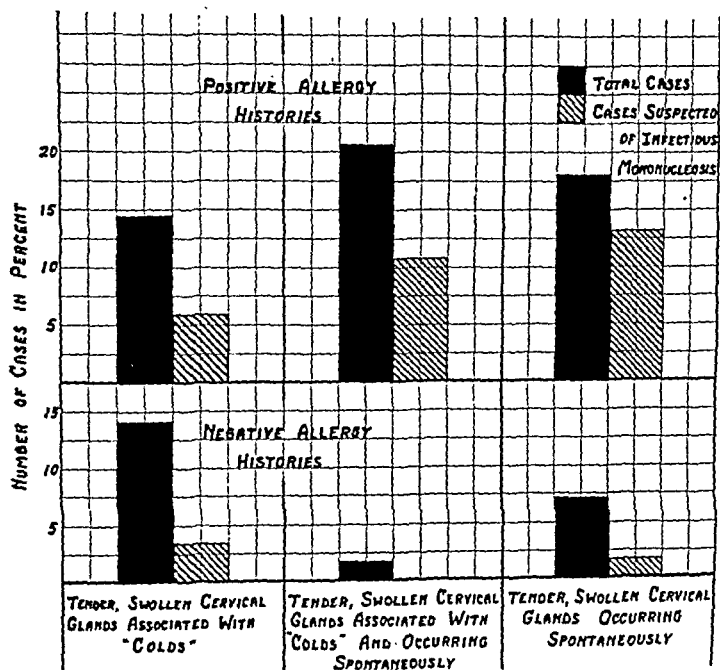


Fig. 2.—The relationship of a history of allergic disease to that of tender, enlarged cervical glands with or without upper respiratory infections and the suspicion of infectious mononucleosis.

Infectious mononucleosis had been suspected in 27 (31.5%) of the 83 cases with a positive allergy history against 2 (3.6%) of those with a negative history; it had been diagnosed on the basis of a positive heterophil antibody determination in 1 case of the former and in 1 of the 2 suspected cases in the latter group. Either the presence of an unexplained fatigue or the history or physical finding of a cervical adenitis had usually suggested the diagnosis. In a smaller number of cases the finding of atypical lymphocytes in the peripheral blood had suggested the possibility of infectious mononucleosis. The history of cervical adenopathy in relation to the suspicion of infectious mononucleosis is shown graphically in Figure 2. As one might expect, those cases having spontaneous or unexplained enlargement of the cervical glands were more commonly suspected of having glandular fever.

Of the 27 individuals having a past history of allergic disease and suspected of having infectious mononucleosis, seasonal or perennial allergic

rhinitis had occurred in 20, recurrent sick headaches in 9, urticaria in 8, bronchial asthma in 6, gastro-intestinal allergy in 6, and atopic dermatitis in 3.

At the time of recording the allergy history, a differential W.B.C. count (100 cells) was obtained. The number of atypical lymphocytes varied from 0 to 22% and bore no constant relationship to the presence or absence of a past history of allergic disease, an average of 5.5% was found in each group. It should be mentioned that the majority of patients with a positive past history of allergy were not having allergic manifestations at this particular time.

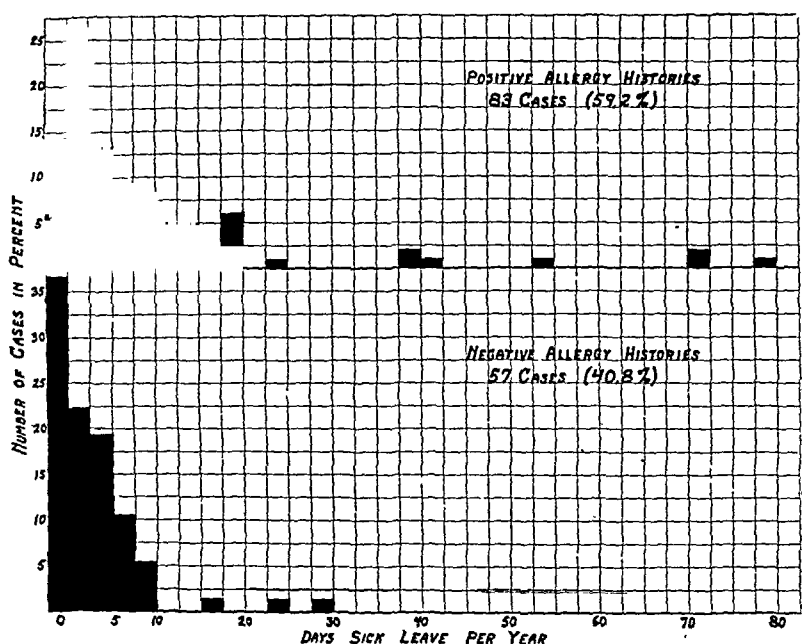


FIG. 3.—Days sick leave per year in relation to the past history of allergic disease.

In reviewing the medical records of this entire series of cases, we were impressed by the relative thickness of the files of the cases with positive histories of allergic disease in contrast to the negative group. It then seemed desirable to determine the amount of time lost per year in each case. Members of the Senior class were followed in this respect for 2 years, the Junior class for 1 year. The results of this survey are represented graphically in Figure 3. Those in the positive group lost on the average of 10.7 days, those in the negative group 3.5 days per year. One striking case in the former series was hospitalized 25 times in a period of 18 months because of undiagnosed allergic headaches. This case was correctly diagnosed later and the headaches were controlled by dietary management.<sup>4</sup> Several cases lost more than 20 days per year as a result of operations, fractures, or severe infections. When the cases of both series who lost more than 20 days per year are deducted, the average time lost by the positive group was 5.8 days against 2.6 days for those with negative past

histories of allergy. Those with no sick leave were more apt to have a negative history of allergy than a positive one.

**Discussion.** The finding of a positive past history of allergic disease in 59.2% of a group of 140 student nurses agrees with surveys conducted by others. Vaughan<sup>10</sup> studied a small community (508 persons) and found that 53.7% had a past history of allergic disease and a questionable history of allergy in an additional 9.8%. Pipes,<sup>3</sup> in a similar survey of 700 individuals of varying age, found an incidence of allergic disease in 44.4%.

To our knowledge, previous surveys have not been concerned with the question of fatigue or variations in the cervical glands in relation to the history of allergic disease.

It is a significant finding that periods of unexplained fatigue occurred in 51.8% of the cases with a positive allergy history, in contrast to 5.3% of those with negative histories. This fatigue, as observed clinically, is not relieved by the usual amount of sleep per night or by obtaining an excessive amount of rest. It is apt to be most marked in the morning, patients frequently volunteering the information that they are more tired upon arising than when they went to bed.

It is suggested that unexplained fatigue is a constitutional symptom of uncontrolled allergic disease, occurring most frequently in association with some definite allergic manifestation. Although frequently observed in cases of allergic intolerance to foods, it is by no means limited to the food allergic response. It is a typical symptom of serum sickness and often persists for weeks after all other evidence of this manifestation has subsided. It is sometimes observed in cases of seasonal hay fever; in occasional cases it may be a more distressing symptom than the rhinitis.

Clinically it is similar to the lassitude occurring in influenza and infectious mononucleosis, in both instances the fatigue may persist for many weeks as the only residual symptom.

The past history of recurrent, swollen cervical glands in 54.2% of the group with positive histories, against 22.2% with negative histories, is also statistically significant. Swollen glands occurring only in association with upper respiratory infections, were present in approximately the same incidence in both the positive and negative series. However, there was a marked difference between the two groups in the incidence of spontaneous attacks of swollen cervical glands. These cases comprise the second and third groups of Figure 2; a past history of allergic disease was the rule, and many of these cases had been suspected of infectious mononucleosis.

The majority of the cases giving a history of tender swollen glands at some time in the past had normal peripheral glands upon physical examination on the date of their history and blood count. A few cases happened to be seen during the course of an upper respiratory infection, some of these were found to have tender and enlarged cervical glands, and a few had a significant number of atypical lymphocytes in the peripheral blood. This response of the blood in the course of an upper respiratory infection has been observed by others.<sup>1,9,11</sup>

A small group happened to have acute allergic symptoms at the time these studies were undertaken. The blood findings in a few of these cases were similar to those previously reported.<sup>5</sup> One patient was seen in consultation 3 months prior to the date of the survey. She complained of a persistent fatigue and rhinitis of 2 months' duration. Differential blood studies revealed 24% of atypical lymphocytes. Another determination 2 days later revealed 12%. She had been hospitalized on 1 occasion 6 months earlier because of unexplained fatigue. While in the hospital, she developed tender and slightly enlarged cervical lymph nodes and a palpable spleen, although her heterophil antibody response was negative. At no time was there evidence of infection to explain these findings. On various occasions she was observed to have an eosinophilia between 5 and 8%. At the time of her survey blood count, she was symptom-free, her lymph glands were normal on examination, and she had only 2% of atypical mononuclear cells in the blood.

The fact that a single blood count failed to show any significant difference in the number of atypical lymphocytes as seen in the positive and negative groups is not surprising. In the first place, the method available for studying the lymphocytes, that is, differential counts from stained film preparations, affords data that is more qualitative than quantitative. Inaccuracies in the enumeration of large cells from either the cover-slip or slide preparations are well known. Repeated determinations in a given case have shown considerable variation in the number of abnormal appearing lymphocytes. In spite of this uncontrollable error in the enumeration of these cells, there is reason to believe that the number of such cells varies from time to time and is apparently dependent upon the presence of lymphoid hyperplasia some place in the body as pointed out by Baldridge, Rohner and Hansmann.<sup>1</sup>

Lymphoid hyperplasia may, in turn, be the result of bacterial antigenic stimulation, such as may occur during the course of an acute upper respiratory infection, or it may be associated with non-bacterial antigenic stimulation as, for instance, in the person sensitized to foods or serum. Rich<sup>6</sup> has emphasized the latter mechanism as a cause of experimentally induced lymphoid hyperplasia in animals.

Clinically there is considerable evidence that, at least in younger individuals, the lymphoid tissue participates in the allergic response. At times of allergic symptoms, examination of these individuals commonly reveals evidence of enlarged peripheral glands; enlarged, edematous tonsils or hypertrophied masses of lymphoid tissue in the posterior pharynx. How frequently the hidden lymphoid tissue of the body, such as that in the gastro-intestinal tract for instance, may participate in the reaction remains speculative. Evidence in support of the concept that the lymphoid tissue participates in the allergic reaction will be presented in detail in another article.

**Summary.** A survey of 140 student nurses showed that 59.2% had a positive past history of allergic disease.

The complaint of "fatigue unrelieved by adequate rest," and the



history of intermittent, "spontaneous" enlargement of the cervical lymph nodes, occurred much more commonly in those with a past history of allergic disease than in the negative controls. This resulted in a diagnosis of infectious mononucleosis being suspected in 31.5% of those with an allergic background, as against 3.6% of those with a negative past history of allergy. Infectious mononucleosis was diagnosed on the basis of a positive heterophil antibody determination in 1 case of each group.

The average number of days sick leave per year in the group with positive allergy histories was over twice that occurring in the group with negative allergy histories.

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### THE USE OF BROMSALIZOL IN LENGTHENING THE EFFECT OF A SYMPATHETIC NERVE BLOCK\*

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In a recent preliminary communication,<sup>4</sup> it was pointed out that mono-brom-hydroxy-benzyl alcohol, more familiarly known as bromsalizol, would block conduction in sympathetic nerve trunks for as long as 8 consecutive days after a single injection. The chemical and pharmacologic properties as well as some of the clinical applications of this drug were described fully in 1934<sup>5</sup> and it need only be mentioned here that its 3 outstanding characteristics are: (a) anesthetic, (b)

\* All the bromsalizol used in this report was kindly supplied by Hynson, Westcott and Dunning, Inc.

antispasmodic, and (c) low toxicity. Because of its low solubility in water, peanut oil was used for a vehicle; a 4% solution of bromsalizol in peanut oil, furnished in 10 cc. glass ampoules, was the standard preparation used for all the observations in this report.

**Technique.** The technique of giving a paravertebral block has been described frequently. The method used for this report was as follows:

Premedication consisted of morphia sulphate 12 mg.  $\frac{1}{2}$  hour before the lumbar paravertebral block was to be given; for the stellate ganglion block, sodium luminal 128 mg. and atropine sulphate 0.6 mg. were substituted for the morphia in order to avoid the small pupil in the test for Horner's syndrome. Atropine was given to avoid a vagal cardiac reflex.

For the lumbar block the patient was placed on his side, the spine of the second lumbar vertebra marked with ink. After skin preparation and draping, a point 4 cm. lateral to the spine and opposite to the side on which the patient was lying was infiltrated with 0.5% procaine, using a fine needle, the anesthetic being then continued to the transverse process where 5 cc. of procaine were placed. A small folded piece of rubber was then pierced with the No. 19 gauge paravertebral needle which was inserted down to the transverse process. The rubber marker was then adjusted so that it was 4 cm. from the skin. With a 10 cc. syringe, containing 0.5% procaine, attached, the needle was lifted well off the transverse process, and directed medially either below or preferably above the process, infiltrating as it advanced toward the body of the vertebra. Once the vertebra was reached, the needle was moved up along it until the anterior psoas fascia was pierced at the vertebra. Ordinarily the rubber marker on the needle would be touching the skin at this point, and when this position was reached 10 cc. of 0.5% procaine were injected followed by one 10 cc. ampoule of bromsalizol. There should be a sudden release or "give" of the needle as it passes over anterior lateral edge of the vertebra. The same procedure was then carried out for the next lower interspace. Only rarely were 3 lumbar segments injected.

In case of the stellate ganglion block, with the patient seated on a stool, 4 cm. were marked off lateral to the vertebra prominens, and at this point a procaine 0.5% injection was carried down to the first rib. The rubber marker was then set at 3 cm. and the needle was directed below the rib and sharply medially along the body of the vertebra until the rubber marker had touched the skin, infiltration taking place constantly as the needle point progressed. Frequent aspirations were necessary to test whether the pleura had been punctured. Once the needle point had reached the desired depth, 10 cc. of 0.5% procaine followed by a 10 cc. ampoule of bromsalizol were injected.

To avoid the possibility of placing oil in the blood-vessels, it was important that repeated aspiration showed no return of blood before the bromsalizol was injected. If bleeding occurred, a small local readjustment of the point of the needle was usually all that was necessary; however, it was occasionally necessary to abandon injection of a particular segment because of hemorrhage.

There are many variations of the above technique. Many physicians avoid the use of a syringe in placing the needle, thus getting a greater delicacy of touch, but sacrificing the benefit of immediate infiltration and aspiration.

Contraindications for the test are a sensitivity to procaine or bromsalizol. So far no routine sensitivity tests have been made before injection. Only 1 case exhibited sensitivity by having generalized dermatitis and hyperpyrexia. This individual later was found to be equally sensitive to peanut oil, as well as to bromsalizol oil by skin tests.

With the above technique, the extremity showed an increased skin temperature by the end of 30 minutes; if bromsalizol alone was used, this effect might not take place for 3 to 7 hours. It was not uncommon for the skin temperature to drop 48 hours after the injection and then to rise again (Fig. 1). Ordinarily in old arteriosclerotic patients the lower extremity would stay warm for 5 consecutive days and gradually get back to normal by the end of the 8th day. However, there were many variations. In patients between 35 and 45 years of age, the effect might last only 3 days. Occasionally there would be an immediate effect lasting a few hours, and then an interval of 1 or 2 days might follow with only intermittent signs of a block, to be supplanted finally by the usual signs which showed that the block had taken effect.

For all practical purposes, simple palpation showed whether the injected side was warm and drier than the opposite side. Inspection of the sole of the foot found this to be redder than its counterpart. Occasionally, skin temperatures were taken with the aid of a thermocouple (Figs. 1 and 2); a few skin resistance determinations were also made. Subjectively, a feeling of warmth throughout the extremity and cessation of pain were frequently mentioned by the patients.

In older individuals, particularly those that have marked arteriosclerosis and are thin, the effect may last 10 days. The longest interval so far observed is in a 70 year old diabetic in whom the first block lasted 6 days, and the second block done over 4 months ago, still shows at this writing a warmer leg on the injected side as determined by the dermatherm, and a block as complete as sympathectomy as established by electric skin resistance measurements. In this patient it is possible that the lumbar sympathetic chain or one or more ganglia were directly infiltrated and possibly damaged by the injection.

Much of the variation in the lumbar blocks may be explained on the accuracy with which the oily bromsalizol is brought in contact with the sympathetic nerve trunk. In obese individuals a thin layer of fat separating the bromsalizol from the chain might explain a poor reaction, even though the aqueous procaine solution had penetrated the fatty tissue more readily, and given an early satisfactory response. In addition, it is known anatomically that there is much variation not only in the number, location and distribution of the ganglia in the lumbar sympathetic chain, but also in the constitution and location of the chain itself.

In all the cases of stellate ganglion block, the results have been better than for the lower extremity. The shortest interval of a dry, warm hand was 17 days; the longest, as vouched for by a letter from the patient, was 1 month.

In a total of 103 patients, there have been 5 failures, probably due to faulty technique. Two were in old men with extensive osteoarthritis of the spine, which increased the difficulty of placing the needle. For the other 3 we have no explanation; possibly the needle was not inserted far enough.

In no case was the use of bromsalizol followed by symptoms of severe peripheral neuritis which not infrequently follows paravertebral

alcohol injections. However, 2 patients complained of a mild burning pain in the groin which disappeared completely in 2 weeks.

To date only 1 patient, a woman of 67 years with diabetic gangrene and osteomyelitis of the tarsal bones, has received as much as 4 paravertebral lumbar blocks. Each subsequent injection had the general effect of the initial block which lasted 9 days. This result has been generally characteristic of all repeat injections.

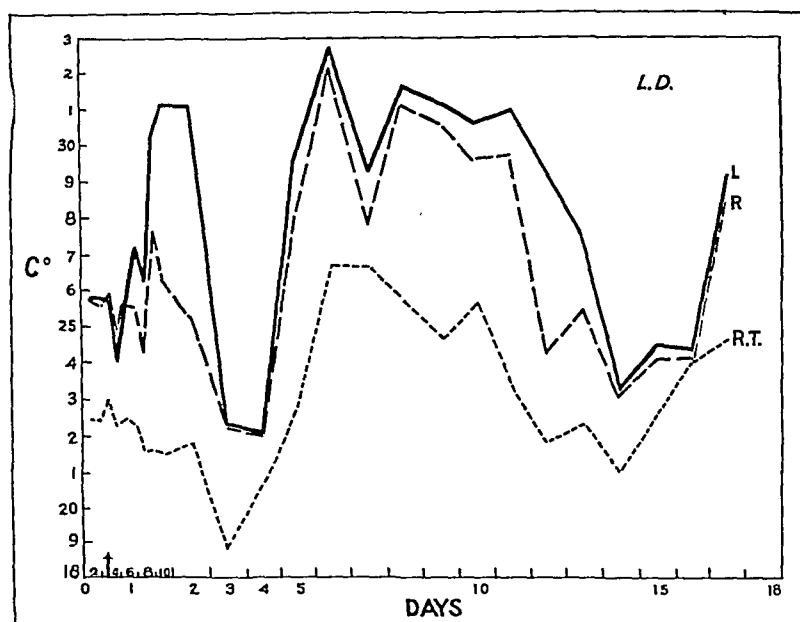


FIG. 1.—The difference in temperature following a left lumbar paravertebral block with 20 cc. of bromsalizol alone. Dermatherm temperature readings were taken from the skin of the plantar surface of the big toe. It will be seen that it took 4 hours before the left big toe became warmer than the right. The subsequent great difference in temperature occurred on the following day, but did not persist. However, another marked difference occurred on the 12th day. There was no consistent great difference in temperature readings. *L.*, left big toe; *R.*, right big toe; *R.T.*, room temperature; the arrow marks the time of the block. All the values were corrected to 29° C. for the constant thermacouple, and to 21° C. for the room temperature.

In this connection it may be mentioned that sympathetic ganglionectomy performed 1 week after a single paravertebral block with bromsalizol showed that the tissue along the chain was mildly inflamed and friable; bleeding was slightly increased. A lumbar ganglionectomy was performed on the patient mentioned immediately above who had 4 paravertebral blocks, and in this instance, the tissues along the chain were extremely friable and suggested the presence of a sterile subacute inflammation.

To rule out the possibility that the results could have been attributable to the procaine and not to the bromsalizol, it is only necessary to say that the first 20 cases were injected with bromsalizol alone and they showed the typical results as mentioned above. In addition the following 2 curves of thermocouple skin temperature readings are given to show that when bromsalizol alone was used, the effect was

essentially the same as when procaine was added to the bromsalizol (Figs. 1 and 2). The chief difference between these 2 curves is the early temporary rise in temperature with the procaine.

Bromsalizol has been used not only for diagnostic purposes in determining collateral circulation and pathways of pain, but also for its therapeutic value. Among the types of cases that were benefited by the injections, the following may be mentioned. But since only relatively few patients have been treated, final evaluation must depend on more cases.

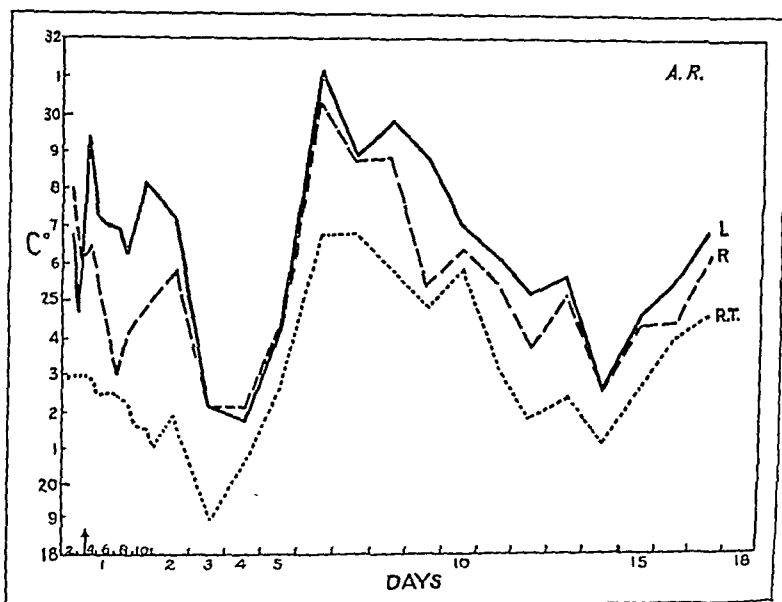


FIG. 2.—The same as Figure 1 except that the paravertebral block was done with 20 cc. of bromsalizol in addition to 20 cc. of 1% procaine. Because of the procaine a prompt difference in temperature was recorded at once. Both patients, L. D. and A. R., were controls, studied at the same time and under the same conditions. L. D., BCH. 81019, a white male, 73 years old, had a fracture of the right tibia; A. R., BCH 86231, a white male, 67 years old, had a right intratrochanteric fracture.

1. *Bromsalizol has been of great benefit consistently in acute thrombophlebitis.*

CASE 1. A. M., a white female, age 17, BCH 87219, was admitted to the medical service on March 31, 1944 with a 3 weeks history of right chest pain, fever, increasing shortness of breath, and cough productive of grossly bloody sputum. The physical findings on admission were compatible with a diagnosis of extensive pneumonic involvement of the right middle and lower lobes, and the left lower lobe of the lungs. Digitalization and oxygen therapy were necessary because of toxic myocarditis with decompensation. She was given sulfadiazine, 6 gm. daily by mouth, with poor response, the temperature ranging between 103° to 104.8° F. the 1st week, and between 100° and 102° F. the 2nd week. The sputum and chest pain disappeared about the 12th hospital day, and the patient was clinically improved. Digitalis and sulfadiazine were stopped during her 3rd hospital week. On the 20th hospital day she complained of pain in the right thigh, and a diagnosis of thrombophlebitis of the deep femoral vein in the upper right thigh was made. Her temperature during the 3rd week ranged between 100° and 101° F. Paravertebral block was performed on the 21st hospital day with novocain and bromsalizol. The symp-

toms rapidly subsided with immediate disappearance of pain which had been excruciating. The tenderness, which was severe, disappeared after 3 days and the edema was only slight after 4 days. The patient's temperature rapidly fell to normal on the 27th hospital day and remained so. Tenderness returned on the 29th hospital day and the patient received a paravertebral block of bromsalizol on the following day. The tenderness disappeared within 24 hours, and the patient was clinically well except for a very slight persistent edema. She was up walking about the ward on the 36th hospital day, and was discharged, walking, May 12, 1944.

In the other cases, only a single injection was necessary, with the exception of 1 patient who required a second injection 9 days later. This use of bromsalizol is in sharp contrast to the more frequent blocks with procaine as advocated by Ochsner and DeBakey.<sup>6</sup> Veal and Hussey<sup>7</sup> even suggested blocks every 12 hours in the acute phase.

2. *Postphlebotic edema following recent thrombophlebitis.* Bromsalizol has been of particular benefit in this group of cases which ordinarily has been treated by compression bandage and elevation of the leg, and only too frequently with indifferent success as evidenced by the enlarged, painful, cold extremity.

CASE 2. A. K., a white female, age 25, was referred by Dr. G. B. Jastram, of Aberdeen, Md., for treatment of bilateral femoral postphlebotic edema. The acute phlebitis involved the left leg from December 16 to December 23, 1943, and the right leg from December 24, 1943, to January 10, 1944. She presented the following symptoms when given the paravertebral block of bromsalizol and novocain on January 30, 1944. There was marked edema of the feet and legs which was less on the left. There was moderate tenderness of the legs and feet which were also cool, moist, and cyanotic. Both legs became warm and dry in 24 hours. The left leg remained so for 10 days, and the right leg for 14 days when sweating of normal character returned. The color of the legs and feet returned to normal in 48 hours and remained so. The tenderness disappeared completely in the left leg and foot in 2 days, and in the right in 4 days, except for very slight tenderness of the right instep. The edema declined rapidly in both legs, and disappeared completely in the left leg and foot after 2 weeks. The edema disappeared from the right leg and foot except for slight swelling of the instep after exercise at the end of 2 weeks. On examination on March 9, 1944, 39 days after injection, after the patient had been on her feet doing housework all day with no elastic support of the extremities, the following was found: The extremities were normal in color, free of tenderness, perspiring normally, and free of edema except for very slight swelling of the right instep.

This paravertebral block was an office procedure; the patient returned home in 1 hour, and assumed her routine duties of housewife in 24 hours. The patient illustrates furthermore the possible economic benefits to be derived from this form of treatment.

In another case, an equally successful result was obtained in a patient who had had edema of a leg 2 months after the acute phase had subsided.

3. *Simple arteriosclerosis has been helped primarily in the healing of ulceration.* In the case of a 73 year old colored man who had had 2 toes amputated at another hospital several weeks prior to admission, and whose ulcer at the operative site had shown no tendency to heal, there was progressive and eventually complete healing after 2 bromsalizol blocks. He was discharged walking on his healed foot.

The symptom of intermittent claudication in arteriosclerotic patients has also been relieved for 10 consecutive days in 3 patients after a single injection.

4. *Arteriosclerosis complicated by diabetes.* This group comprises 3 cases, all of whom were far advanced in the healing stage, and none required amputation. The following case illustrates this group.

CASE 3. J. S., a white male, age 70, BCH 87744, was admitted to the Baltimore City Hospitals December 30, 1943, with a diabetic ulcer in a large callus over the head of the second metatarsal of the right foot, and a cellulitis extending to the knee. A posterior tibial artery pulsation was present but the dorsalis pedis artery was not palpable. A paravertebral block with bromsalizol and novocain was given on December 30, 1943, and the leg was placed in warm moist compresses. On the following day the sole of the foot was incised through the callus and a large pocket of infected gangrenous tissue opened. Three days later, because drainage was inadequate and the second toe had become obviously gangrenous, a second operation was performed in which the second toe was disarticulated and the plantar incision was carried toward the heel until good tissue was reached. Compresses were discontinued on January 4, 1944. The paravertebral block was repeated with bromsalizol and novocain on January 5, 1944. His temperature ranged between 99.8° and 101° F. for 4 days, then gradually fell to normal on the 7th hospital day, and except for occasional slight elevations, remained there throughout his hospital stay. The right leg stayed continually warmer than the left, and it was not necessary to repeat the paravertebral block after the second one. The necrotic tissue gradually sloughed with the use of azochloramide irrigations and compresses, and the area of incision healed except for a small draining sinus beneath the second and third metatarsal heads which appeared to be coming from the infected flexor tendon of the third toe. The patient was discharged walking on February 23, 1944, and worked as a drug clerk from 5 to 7 hours daily, being dressed at weekly intervals in the Out-Patient Department. The sinus persisted, and Roentgen ray picture on April 25, 1944 revealed involvement of the metatarsophalangeal joint of the third toe. The patient was readmitted to the hospital on May 2, 1944 and on May 4 the third toe and distal one-half of the third metatarsal bone were excised under spinal pontocaine anesthesia. Following this, the wound healed rapidly and the patient was discharged walking on May 12, 1944 with the wound well healed. The right leg was tested against the left with the dermatherm and found to be much warmer, indicating a persistence of effect of the last paravertebral block on January 5, 1944. The patient stated that he had noticed that the right leg had been continually warmer than the left. Skin resistance measurements were made on May 12, 1944; they confirmed the dermatherm readings and indicated a complete sympathetic block with some spread to the left buttock.

Because of the success of the bromsalizol blocks, the patient has so far been spared a lumbar sympathetic ganglionectomy and possibly a major amputation.

5. *Bromsalizol has been helpful in cellulitis in the feet of arteriosclerotic patients.* It has also aided in limiting the area of gangrene and speeding the process of demarcation.

6. *Bromsalizol has been helpful in healing amputation stumps.* In the case of a Negro 82 years old with gangrene of the toes of the right foot, a Symes amputation of the foot after a bromsalizol lumbar sympathetic block was attempted. Healing almost succeeded. However, an amputation below the knee was performed later; the incision over the fibula broke down but healing eventually occurred after

repeated bromsalizol blocks. In another case, amputation of the second toe for an indolent arteriosclerotic ulcer at the first interphalangeal joint was followed by healing after a bromsalizol block. In 2 cases, healing of the stump in a supracondylar amputation after lumbar sympathetic blocks seemed to take place more quickly than usual.

7. *Two cases of frostbite were treated by bromsalizol blocks.* In 1 patient, a 33 year old colored male, who had bilateral frostbite and gangrene of the tips of all toes, with the right foot worse than the left, received one lumbar bromsalizol block on the right side. The left side was not blocked, and was used as a control. Healing on the right side was faster than the left even though this side was more severely damaged originally. Eventually only the tips of the toes of both feet were lost.

8. *Thrombo-angiitis obliterans.* Only 1 case was seen.

CASE 4. I. M., Johns Hopkins Hospital, No. 318984, a 35 year old, active, non-smoking Jewish business man was referred by Dr. Lay Martin, Baltimore, Md., with symptoms of moderate intermittent claudication in both legs, worse on the left. Immediately after the bromsalizol block on the left side, symptoms came on as before when he walked, but the pain subsided more quickly. On each of the two following days he walked a mile with the usual discomfort on the right side but none on the left. A report received 5 weeks later showed that he still had some benefit from the block. Whether repeated blocks will let him escape lumbar sympathectomy is still problematical.

9. *Arterial occlusion.* In 2 cases of femoral arterial embolism, a single lumbar block with bromsalizol gave complete relief from pain for 13 days in 1 case and only moderate relief in the other instance. Two cases of arterial thrombosis were treated with similar results. There were also single instances of venous clinical pictures which were treated.

The following single instances are worth recording.:

10. *Angina pectoris.* A patient, F. P., 49 years old, referred by Dr. N. B. Herman, Baltimore, Md., with symptoms of angina pectoris, and with myocardial damage as shown by the electrocardiogram, received a bilateral block of the stellate ganglia with bromsalizol; bilateral enophthalmus was present for 2 days, the right hand remaining warm and dry for 17 days and the left hand for 30 days.

Obviously nothing can be claimed for bromsalizol in this instance even though 4 weeks later he could walk a half a mile in reasonable comfort after having been virtually bed-ridden before. Even though the function of the sympathetic nerves with reference to the coronary arteries is still not firmly established,<sup>1,3</sup> the possibility exists that useful information may be obtained from these paravertebral blocks.

11. *Dermatitis.* A case of infected atrophic eczema of both legs seen in consultation with Dr. J. Ralph Horky, Churchville, Md., was treated by a bilateral bromsalizol block. The infection immediately subsided, and improvement was sustained for 1 month when another block was given with equally good results.

12. *Obstetrics.* To relieve the pain in childbirth the method of Jarvis,<sup>2</sup> who used frequent paravertebral blocks of procaine, was supplemented by the addition of bromsalizol. The results so far have



not been clear-cut enough to report, but the indications are that much of the pain in the first stage of labor can be relieved by a single injection.

13. *Unexplained pain.* In a man of 59 years, with bilateral unexplained stabbing pains in the calf, sole, and toes of both legs, worse on the right, a bromsalizol block was given first in the right side. He obtained such marked relief that he insisted on a block for the other side. He has not had a return of pain to date, namely, 4 months after the initial block.

Stated simply, bromsalizol does no more than the ordinary procaine paravertebral block except that the effect is longer, even though the intensity is not as great (Figs. 1 and 2). However, there is the possibility that in certain fortunate injections like the 2 mentioned above in which the effect was still present 4 months later, that the needle point actually damaged the sympathetic trunk. Only further observations will be able to establish how long such a block will remain, but for the present it can be stated that a bromsalizol block seems to have accomplished for 4 consecutive months as much as could have been expected from a lumbar sympathetic ganglionectomy.

It is possible that bromsalizol may be of value in two large groups of cases. In the first instance, by preventing vasoconstriction and thus providing better circulation, the drug might improve any inflammatory process anywhere in the body. In injuries of the extremities in war and industry, when prolonged relief of vasospasm may save the extremity, bromsalizol may have its place. In the second instance, by blocking the pathway of pain along the sympathetic trunk, it might bring relief to cases of dysmenorrhea, causalgia, or inoperable malignant tumors. Any condition which has not been benefited by sympathetic ganglionectomy would probably not be helped by bromsalizol.

In general, the entire field of peripheral anesthesia so far has been limited essentially to its two extremes—either a short temporary phase, or a permanent nerve paralysis. Apparently there is no intermediate interval between the anesthesia of a few hours as given by a host of substances, and the permanent loss of conduction by destroying the continuity of a nerve either by the scalpel or alcohol injection. An exception may be made in the case of the proctologists who have tried many drugs and chemicals, such as quinine and urea, to bring relief for longer periods in such conditions as pruritus ani. What is badly needed is an anesthetic which is operative for days and possibly months. Bromsalizol may prove to be an entering wedge. It apparently has no paralyzing effect on the human peripheral somatic nerve, because in 2 patients the ulnar nerve at the elbow was bathed in 10 cc. of the preparation without any sign of an ulnar nerve paralysis.

Experimentally, the effect of bromsalizol on the peripheral sympathetic system of dogs showed an entirely different reaction than had been expected. In 2 dogs, the vagus nerve, which carries with it the cervical sympathetic trunk in the neck, was freed widely from the common carotid artery under surgical conditions. The wound was filled with 5 cc. of bromsalizol which completely surrounded and bathed the nerve. However, no constricted pupil as a sign of Horner's syn-

drome appeared. In 4 instances, the chest was opened aseptically in the second interspace, and 5 cc. of bromsalizol was injected in the region of the stellate ganglion. Again no Horner's sign was seen. In a 5th case, the sign did appear within 12 hours and has persisted for 20 days. In a 6th dog, 10 cc. of bromsalizol was injected, and also no Horner's sign was obtained. Whether the needle point damaged the stellate ganglion in the 1 case in which a small pupil resulted, cannot be determined at present. In 2 more animals the chest was opened under sterile precautions, and the stellate ganglion was freely exposed after stripping away the pleura. Ten cc. of bromsalizol were then injected all around the ganglion. Again there was no evidence of Horner's sign. At all events, it seems as if bromsalizol affects the human but not the canine peripheral sympathetic system. The reasons for this difference are open to investigation.

Furthermore, the marked difference in effect as between man and the experimental animal naturally brings up the question as to the extent to which it is justifiable to expect similar reactions in the two groups. It may well be that certain drugs and chemicals may have a profound effect on man without affecting the experimental animal. On this basis alone, many substances anesthetic to man may have been discarded because they had no effect on the experimental animal.

**Summary.** A 4% solution of mono-brom-hydroxy-benzyl alcohol (bromsalizol) in peanut oil was used for paravertebral blocks of the sympathetic nerve trunks of 103 patients.

It was found that the blocks with this drug gave a much longer beneficial effect than with the usual procaine. In old arteriosclerotic patients the effect of a lumbar block would last for 5 consecutive days and then gradually disappear by the 8th day. In 2 cases, the block was still effective after more than 4 months. In younger patients the effect might last only 48 hours. In 5 cases no effect was obtained.

The stellate ganglion block in the 4 available instances lasted from 17 to 30 days. It was much better than the lumbar block.

The best results were obtained in cases of femoral thrombophlebitis; a single injection was usually sufficient for the acute phase, and in 2 cases treated immediately after the acute stage, a single injection was enough to reduce the swelling almost entirely.

By improving the circulation, bromsalizol has been successfully used therapeutically in cases of diabetic ulcers and gangrene, in cellulitis of the foot, in frost-bite, in amputations below the knee, in temporarily relieving the pain of intermittent claudication in arteriosclerosis and thrombo-angiitis obliterans, in arterial vasospasm, and in temporary relief from dermatitis.

Bromsalizol has been used diagnostically as a clinical test for collateral circulation.

Bromsalizol was injected around the ulnar nerve without causing any signs of nerve paralysis.

In dogs, bromsalizol did not produce a Horner's syndrome when injected around the stellate ganglion.

It is a pleasure to make the following acknowledgments. The facilities for the animal experimentation in the Surgical Hunterian Laboratory were extended by Dr. Alfred Blalock, Professor of Surgery at the Johns Hopkins Medical School; the dermaterm was loaned by Dr. Arthur M. Shipley, Professor of Surgery at the University of Maryland; the skin resistance measurements were made by Mrs. Woodruff and Miss Evans of Dr. Curt P. Richter's Psychobiological Laboratory, Johns Hopkins Hospital.

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## SPERMATOGENIC ACTIVITY OF VARIOUS STEROIDS\*

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NUMEROUS experiments<sup>3,6,9,10,15</sup> have shown that testoid substances, as well as anterior pituitary gonadotropins, inhibit testicular atrophy in hypophysectomized rats. More recently, Albert and Selye<sup>2</sup> and Selye and Friedman<sup>13</sup> reported that steroids devoid of testoid potency such as  $\Delta^5$ -pregnenolone and progesterone exhibit spermatogenic activity. These conclusions were confirmed with  $\Delta^5$ -pregnenolone by Ruzicka<sup>11</sup> and Leatham and Brent.<sup>5</sup> The latter showed furthermore that ethynyl-testosterone, which like progesterone produces marked progestational changes in the rabbit, is completely inactive in this respect.

At first Nelson and Merckel<sup>10</sup> claimed that male hormone preparations as well as testoids were unable to reinitiate spermatogenesis in adult rats which had been hypophysectomized for several weeks. However, in subsequent publications<sup>7,8</sup> they rectified their statement, indicating that if an adequate dosage is given, sperm formation is restored even if the treatment be started 22 to 28 days after the operation. Similarly, Cutuly *et al.*<sup>3,4</sup> found that spermatozoa may occur in the seminiferous tubules of immature hypophysectomized rats treated with testosterone propionate and "dehydroandrosterone acetate."

Unfortunately some of these data are not of great value for comparative purposes because the authors used either impure urinary

\* The expenses of these experiments have been defrayed by a grant from the Gelatin Products Company, Detroit.

extracts or insufficiently described compounds. Since only common names such as androstenediol (trans) or dehydroandrosterone were mentioned, and no melting points given, it is difficult to determine the exact nature and the degree of purity of these preparations.

In the present paper we wish to report on a series of investigations in which 16 steroids were tested under identical conditions in hypophysectomized animals.

**Methods.** All our experiments were performed on immature male albino rats weighing 40 to 60 gm. (average 50 gm.) at the onset of the experiment. They received the compounds to be tested in 0.1 cc. of oil subcutaneously twice daily for a period of 10 days, injections being started the day following hypophysectomy. All the steroids were given in the dose of 2 mg. per day, except for  $\Delta^5$ -pregnenolone, which was assayed at 2-dose levels: 2 mg. and 1 mg. A diet consisting mainly of "Pablum"\* mixed with milk was found to be very satisfactory to maintain the animals in good condition. On the 11th day the rats were weighed and autopsied; the genital organs were removed and fixed in Suza for subsequent weighing and histologic study. Two criteria were taken for spermatogenic activity: the testis weight and the presence of spermatozoa in the seminiferous tubules. To ascertain the completeness of hypophysectomy, the following points were considered: absence of pituitary remnants visible with magnifying glasses, a body weight increase of less than 10 gm., adrenal weight of less than 10 mg., and atrophy of the accessory sex organs in the case of steroids known to be inactive as testoids.

Three groups of animals were taken as controls: the animals of Group 1 were non-operated and sacrificed at the beginning of the experiment; those of Group 2 were non-operated and kept for a period of 10 days; and finally those of Group 3 were hypophysectomized and treated for 10 days with cholesterol, substance devoid of any pharmacologic activity.

**Results (Table 1).** The steroids are arranged according to decreasing testicular weight. It will be noted that the testis weight of animals treated with active compounds is more nearly comparable to that of control Group 1 than of control Group 2. Therefore, none of the steroids so far studied is able to promote a normal growth of the gonads in the absence of the pituitary. On the other hand, the results of the histologic study show that spermatozoa are present in some experimental groups and control Group 2, while none could be detected in control Group 1. It seems evident that no relationship necessarily exists between the weight of the testis and the activity of the germinal epithelium. This is also substantiated by the fact that, in experimental groups having approximately the same average testis weight, some showed spermatozoa in more than one-half of the animals (androstenediol dipropionate and methyl androstenediol), while the others were negative (methyl testosterone and testosterone). In the case of the latter compounds there was, however, evidence of stimulation. Contrary to our findings, Cutuly *et al.*<sup>3,4</sup> reported that testosterone propionate induces sperm formation; a very likely explanation is a longer duration of treatment and the use of an ester instead of the free compound.

Selye<sup>12</sup> considered the prospermatogenic effect of the steroids as an independent pharmacologic activity. The present experiments confirm this conclusion. Although most of the active steroids stimulate

\* Prepared by Mead Johnson & Co., of Canada, Ltd.

the accessory sex organs, as can be seen in the weights of the seminal vesicles and prostate, there is however no direct relationship between the testoid and the spermatogenic activity: androstenediol and its dipropionate, and  $\Delta^5$ -pregnenolone have a very marked effect on the testis, although their testoid activity is moderate or *nil*. The spermatogenic activity is not subordinate to the luteoid activity: progesterone, methyl androstenediol, desoxycorticosterone acetate and ethynyl testosterone possess a strong progestational effect,<sup>14</sup> but the first 2 are active and the last 2 inactive on the testis. Obviously it is not subordinate to the folliculoid or corticoid activity.

TABLE 1.—EFFECTS OF VARIOUS STEROIDS ON THE TESTIS, PROSTATE AND SEMINAL VESICLES OF HYPOPHYSECTOMIZED IMMATURE RATS

Name of compound	M. p. (°C.)	No. of rats	Testis (mg.)	Seminal vesicles (mg.)	Prostate (mg.)	Spermatozoa*
$\Delta^5$ -androstene-3( $\beta$ ),17( $\alpha$ )-diol dipropionate	119-120	7	381 (183-495)	25.1 (17.5-34)	63.8 (50.6-102)	+(5) 0(2)
17-methyl- $\Delta^5$ -androstene-3( $\beta$ ),17( $\alpha$ )-diol	203-204	5	378 (310-449)	152 (123-179)	157 (129-184)	+(4) 0(1)
17-methyl-testosterone . . . . .	164.5	7	364 (190-490)	165 (153-190)	156 (135-163)	0
17-methyl-androstane-3( $\beta$ ),17( $\alpha$ )-diol . . . . .	211-213	6	329 (263-480)	153 (132-188)	159 (130-201)	+(1) 0(5)
$\Delta^5$ -androstene-3( $\beta$ ),17( $\alpha$ )-diol . . . . .	182-183	14	321 (195-490)	83 (62-103)	112 (96-145)	+(2) 0(12)
Testosterone . . . . .	152-153	7	310 (210-420)	143 (80-190)	187 (136-275)	0
$\Delta^5$ -pregnenolone† . . . . .	187-189	9	292 (138-458)	4.1 (3-6.7)	27.6 (22-37)	+(3) ±(1) 0(6)
$\Delta^5$ -pregnenolone‡ . . . . .	187-189	8	241 (82-418)	3.6 (2.3-6)	16.9 (7.6-26)	0
Progesterone . . . . .	129	6	260 (180-380)	5.3 (3-9)	42 (32-77)	0
$\Delta^4$ -androstenedione . . . . .	168-169	6	253 (130-308)	46.8 (32-73.4)	104.8 (45.7-160)	0(6)
Dehydroisoandrosterone . . . . .	146	9	222 (96-310)	5.7 (4-10)	36.4 (17-53)	+(2) 0(7)
Ethynyl testosterone . . . . .	265-267	11	116 (84-160)	24.1 (14-64)	43.3 (22-81)	0(11)
Desoxycorticosterone acetate . . . . .	154-155	10	113 (76-180)	3.9 (2.6-6)	17.8 (9-19)	0(10)
Acetoxypregnenolone . . . . .	182-183	7	109 (78-194)	2.7 (2.4-3.6)	11.4 (6.3-15.4)	0(7)
Cholesterol . . . . .	149	11	105 (73-128)	3.7 (3.3-5)	10.2 (6-13.6)	0(11)
Control group I . . . . .	...	10	306 (193-430)	5.1 (3.3-7)	29 (16.4-43)	0(10)
Control group II . . . . .	...	10	878 (725-1170)	10.9 (8-16)	57 (42-69)	+(10)

Results of histologic examination to determine presence of spermatozoa are indicated by the following symbols:

\* + positive, ± doubtful, 0 negative. The numbers in brackets refer to the number of animals in the case of various responses within the same group.

† 2 mg. per day.

‡ 1 mg. per day.

It is interesting to note that Albert and Selye,<sup>1</sup> from their studies on the gonad-protecting activity of steroids against atrophy caused by estradiol, obtained results identical to our own. Evidently any steroid possessing spermatogenic activity is able to inhibit the testis atrophy resulting from hypophysectomy or treatment with folliculoids.

**Summary and Conclusions.** The spermatogenic activity of 16 steroids was studied in immature hypophysectomized rats, taking as criteria the testicular weight and the presence of spermatozoa in the seminiferous tubules. Among these the most active compounds are androstenediol dipropionate, methyl androstenediol,  $\Delta^5$ -pregnenolone, methyl androstenediol, androstenediol, and dehydroisoandrosterone. It is definitely established that the ability of steroids to protect the testis against the atrophy caused by hypophysectomy is entirely independent of the other main pharmacologic activities.

The author is greatly indebted to the following chemists, who kindly supplied the steroids used in this investigation: G. W. Holden of Charles E. Frosst & Co., E. Pike of Gelatin Products Co., C. Scholz of the Ciba Co., and E. Schwenk of the Schering Corp.

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### MEIGS' SYNDROME IN A CASE OF MULTIFOCULAR PSEUDO-MUCINOUS CYSTADENOMA OF THE OVARY\*

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THE association of fibroma (or fibromyoma) of the ovary with hydroperitoneum and hydrothorax has received increasing attention in the last few years, especially since the classical reports defining this condition were first published by Meigs and Cass<sup>23</sup> in 1937 and by Meigs<sup>19</sup> in 1939. This is demonstrated by the fact that while only scattered

\* Believing that, in general, eponymic names of diseases should be restricted closely to the conditions as described by the original author, we asked Dr. Meigs if he thought that the term was justified in this case, which is not a fibroma, as originally described by him. We may say that he thinks that it is justified, and that the various types of primary lesions should be considered, from this point of view in one group. This seems desirable, as the secondary changes—effusions into the serous cavities—are the same following various neoplasms, the leak occurring in an organ without a good capsule.—EDITOR.

reports on authentic cases can be culled from the literature between 1879 and 1934, hardly a year has passed since 1937 without reference in some American journal to new cases of ovarian fibromata associated with abdominal ascites and pleural effusion. This clinical entity has appropriately been given the name of "Meigs' syndrome."

The association of benign ovarian tumors other than fibromata with ascites and hydrothorax is also beginning to be reported. Thus Vogt<sup>32</sup> reported a case of granulosa cell tumor of the ovary associated with hemoperitoneum and hemothorax. Traut and Marchetti,<sup>31</sup> analyzing a group of 61 tumors of the "granulosa" type and "theca" cell type for the Society of Gynecological Pathologists of New York, state that, in one of the cases presented, hydrothorax was a prominent symptom and that on operation abdominal fluid was found. The tumor of the ovary proved to be quite benign. McFee<sup>17</sup> reported a case in which a multilocular cystadenoma of the left ovary weighing 17 pounds was found associated with abdominal ascites and hydrothorax. Perlmutter<sup>25</sup> observed this same syndrome where a thecoma of the right ovary was later found at operation. Kelemen<sup>13</sup> has recently reported a case due to a Brenner tumor of the ovary.

In addition, it has been found that benign tumors of the pelvic organs, other than those of ovarian origin, can give rise to the symptom-complex of abdominal ascites associated with pleural effusion. In a personal communication to Meigs,<sup>22</sup> Cullen states that a case of uterine fibroids associated with abdominal and chest fluid<sup>14</sup> referred to in his textbook would, in the light of our present knowledge, fall into this category. Salmon<sup>29</sup> in addition to 1 case of ovarian fibroma with fluid in the peritoneal and pleural cavities, reported a case in which fluid was found in these cavities in association with a large uterine fibroid with interligamentous extension and follicular cysts of the ovaries.

Agreeing with the following statement: "The importance to the internist, as to the gynecologist, of keeping in mind the fact that a benign ovarian tumor may cause hydrothorax as well as ascites and that the simplest of laparotomies uniformly results in complete relief of the thoracic as well as of the abdominal features of the syndrome needs general recognition and emphasis" (Herrick *et al.*<sup>10</sup>), we herewith report a case of pseudomucinous multilocular cystadenoma of the ovary associated with hydroperitoneum and right hydrothorax. In common with all the cases mentioned above, regardless of the origin or of the cellular structure of the benign pelvic tumor, complete cure was obtained in this case. The tumor was removed with subsequent complete recovery of the patient and disappearance of the fluid. This is the true test for a case of Meigs' syndrome.

**Report of Case.** H. R. (No. 21709), a 39 year old white female, admitted on May 24, 1943, discharged on June 10, 1943, on May 22, 1943, presented herself at the office of one of us (J. M.) with the complaint of shortness of breath on mild exertion. Examination revealed fluid in the right chest from apex to base (confirmed by fluoroscopy), and an enlarged abdomen. Her weight was 135 pounds. Hospitalization was advised, and the patient was admitted to the Mercy Hospital, Rockville Centre, L. I., N. Y., 2 days later.

For 6 to 8 weeks the patient had been complaining of increasing shortness of breath with dry cough in the last 2 weeks. An incidental complaint was the loss of 12 pounds, which the patient states was due to a self-imposed diet, and which she regained recently. The past history revealed that the patient had had bronchitis the winter before. She had 2 children, aged 10 and 17 years. There was no history of miscarriage. The family history was non-contributory.

System review revealed the absence of gastric distress, the appetite to be good, and the bowels regular. On coughing there was no mucus or bloody expectoration, or chest pain. Peripheral edema was absent. Menses were regular with the exception of February, 1943, when she had a period twice in 1 month. There were no urinary disturbances.

The patient sat quietly in bed with a somewhat drawn expression; her face thin, but general nutrition was good. The chest revealed absent breath sounds from apex to base, and dullness to percussion in the right chest. The heart was shifted to the left. The rhythm was regular and there were no murmurs. The blood pressure was 110/70. The abdomen revealed a mass filling the pelvis and extending up to the umbilicus. The cervix was freely movable and the ovaries were not felt.

A diagnosis of malignant neoplasm in the pelvis with metastasis to the right pleural cavity was made. The surgical consultant (J. S.) agreed, and exploratory operation was advised after removal of the chest fluid.

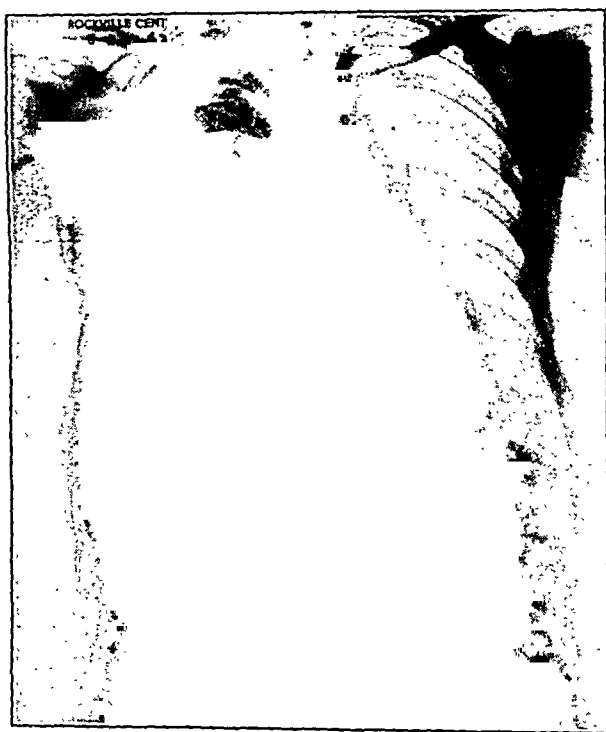


FIG. 1.—Roentgen ray of chest on admission to Mercy Hospital.

*Course.* The patient had no fever on admission. The urinalysis and blood count were normal. On the day of admission 900 cc. of straw-colored fluid was withdrawn from the chest and sent to the laboratory for examination.

*Roentgen ray Report* (5/24/43). There is a large amount of free fluid in the pleural space on the right, extending from the level of the diaphragm to the apex. There is a zone of aerated lung at the right of the spine. The mediastinal structures and the lung root are displaced toward the left. There is no evidence of disease of the lungs. There is no destructive bone disease.



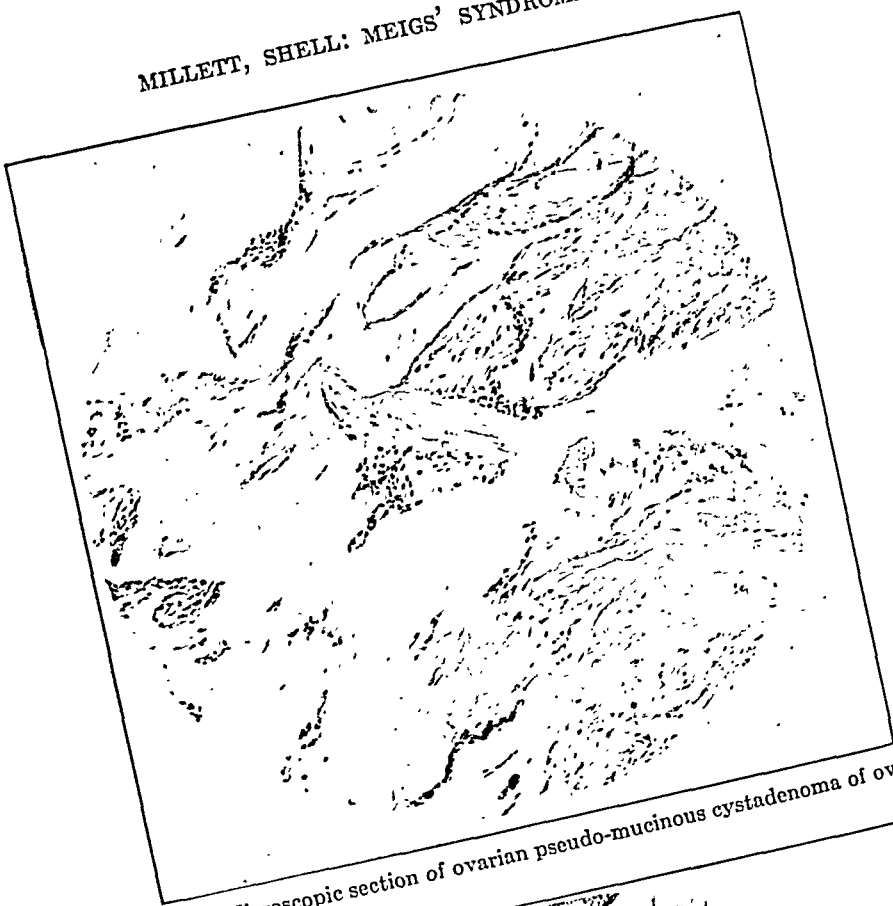


FIG. 2.—Microscopic section of ovarian pseudo-mucinous cystadenoma of ovary.

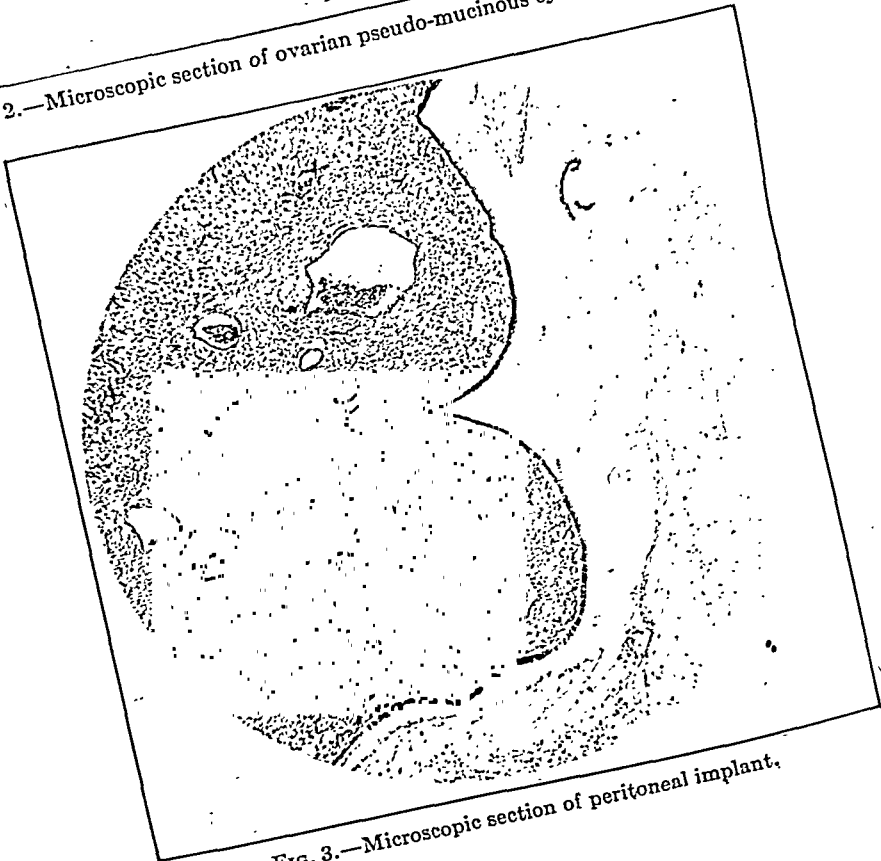


FIG. 3.—Microscopic section of peritoneal implant.

*Laboratory Report on Fluid.* Smear: no evidence of bacteria. Culture: no growth. Diagnosis: non-malignant transudate.

On May 25, 1943, 900 cc. of chest fluid was removed. The patient broke out into a light warm sweat, and although no discomfort was complained of, the tap was stopped. On May 27, 1943, 1950 cc. of chest fluid was removed without the patient experiencing any discomfort.

*Laparotomy* (J. S.) (May 28, 1943). A large ovarian cyst was delivered without difficulty. There was a moderate amount of yellow peritoneal fluid, and occasional mucinous implants were noted on the peritoneal surfaces. One peritoneal implant was removed for pathologic examination. The postoperative course was entirely uneventful. The patient ran a temperature of 100° (R) for 2 days. This subsided on the 3rd postoperative day and remained normal for the rest of the stay in the hospital.

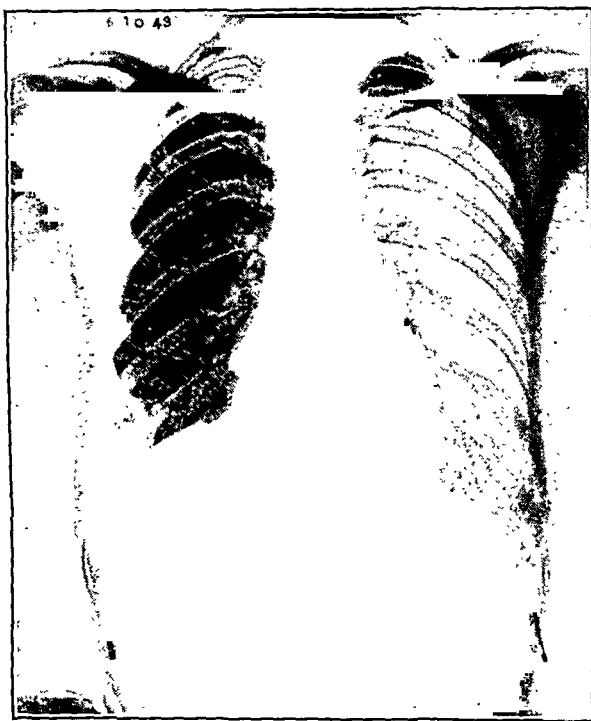


FIG. 4.—Roentgen ray of chest on discharge from Mercy Hospital.

*Pathologic Report.* On A, Cyst; B, on peritoneal implant.

A. Specimen consists of a massive ovarian cyst previously sectioned and now showing an interior consisting of numerous locules containing a thick mucilaginous fluid. The attached tube is somewhat elongated and on section shows no noteworthy change. The cyst wall shows numerous small secondary cystic implants.

B. Specimen consists of a small pea-sized mass having a finely villous-appearing outer surface rich in mucinous material.

Diagnosis: A. A multilocular pseudomucinous cystadenoma of the ovary. B. Peritoneal implantation of tumor tissue. (Dr. Theodore J. Curphey.)

On June 10, 1943, 700 cc. of straw-colored fluid was obtained from the right chest and taken to the laboratory for examination. The guinea pig test for tubercle bacilli, reported several weeks later, was negative.

*Roentgen ray Examination* (6/10/43). Reëxamination of the chest after 2 weeks and after the removal of 700 cc. of fluid reveals no evidence of free

fluid in the pleural space. On the right the apex is retracted and there is a small pneumothorax in this area. The interlobular fissure on the right is faintly outlined. The right diaphragm is elevated and tented in its median portion by a pleural adhesion. There is no evidence of metastatic disease in the lung fields.

The patient was discharged on the same day. Her weight was 109 pounds. She was last seen in April, 1944 at which time the pelvic examination was negative and the chest was free of fluid by physical examination and fluoroscopy. Her weight was then 137 pounds, and she felt and looked the picture of health.

**Comment.** Meigs' syndrome can be regarded by definition as a simultaneous collection of abdominal and chest fluid due to a benign tumor of the pelvic organs.

The etiologic factor is usually a benign fibroma of the ovary; but it can also be a granulosa cell tumor, a cystadenoma, thecoma, or Brenner's tumor. Grossly, these ovarian tumors producing the fluid may vary in size from that of a small orange to that of a 4 to 5 months pregnant uterus. Microscopically, they are usually derived from the various connective tissue elements of the ovary. In none of these cases are any malignant elements found. Rarely benign fibromyomata of the uterus may be a cause.

The production of fluid by these smooth-shelled tumor masses has never been satisfactorily explained. The frequency of abdominal ascites by itself in these cases varies with the series reported, but occurs on the average in about 20% of cases.<sup>6,11,26</sup> In conjunction with chest fluid the percentage must be much less. A recent clinical and pathologic study of 283 cases of ovarian fibromas at the Mayo Clinic by Dockerty and Masson<sup>14</sup> revealed 3 cases of Meigs' syndrome. Inasmuch as inflammation, pedicle twists, and omental adhesions are infrequently found with these tumors in association with the fluid, and inasmuch as the fluid disappears on removal of the tumors, one must agree with Meigs<sup>22</sup> that there is cause and effect in this connection.

Meigs has proved that the flow of fluid is from the abdominal cavity to the pleural cavity by injecting India ink into the peritoneal cavity of patients with Meigs' syndrome and finding it in the chest fluid in the same concentration later. Following the injection of India ink into the chest cavity, none was found in the abdominal fluid. In addition, he injected air into the chest cavity of one of his patients and tilted her in the Trendelenburg position. After numerous Roentgen rays in various positions, no air was noted in the abdominal cavity. Ritvo reversed this procedure by injecting air into the abdominal cavity by means of a peritoneoscope and noted that no air found its way into the pleural cavity. One may thus rule out pleuro-peritoneal openings in the diaphragm. At present, until further experimental findings prove otherwise, abdominal fluid may be assumed to reach the pleural cavity by way of the lymphatics. Some additional weight to the assumption that abdominal fluid is the source of the chest fluid is that in 2 of Meigs' cases the abdominal fluid and the chest fluid

were identical as to total protein content and as to the electrophoretic distribution of the protein components, namely albumin, alpha, beta, and gamma globulins, and fibrinogen.

Clinically the patient presents a variety of symptoms and a few outstanding physical signs. She is anywhere between 34 and 75 years of age. Her occupation is not significant from a medical viewpoint. The complaints may be of recent origin or they may have been present for years with a recent history of having become worse. The gastrointestinal history is usually that of vague appetite disturbances with perhaps occasional bloating and belching. There is occasional constipation but no diarrhea. The menstrual cycle is apparently not usually disturbed. Rarely is there irregular bleeding either before or after the menopause has set in. She may or may not have had children. One case is reported to have associated with pregnancy and the patient died.<sup>3</sup>

The patient may appear well nourished or she may state that in spite of maintaining her normal weight or even gaining weight, her face looks thin. She may appear acutely, chronically, or gravely ill. Complaints referable to the chest are dyspnea, gradually increasing, either at rest or on moderate exertion. Orthopnea is a prominent symptom. Chest pain is rare, although a "heaviness" in the chest may be felt. Abdominal complaints are usually those of enlargement, with probably bearing down or heavy sensations in the pelvis. Backache and frequency or difficulty in voiding may be experienced. Due to elevation of the diaphragm there may be respiratory embarrassment. Occasionally a history of repeated chest or abdominal taps or both with rapid reaccumulation of the fluid will be obtained.

Important in the diagnosis of Meigs' syndrome is the finding of chest fluid and the finding of an abdominal tumor in association with ascites. Frequently abdominal paracentesis may be necessary before a small or moderately sized tumor can be felt on bimanual examination. Sometimes all that is felt is a large tumor mass, and a moderate amount of fluid will be found in the abdominal cavity on operation entirely out of proportion to the massive amount in the pleural cavity. Frequently all that the patient will complain of is dyspnea. An abdominal tumor will be missed because attention is drawn to the pleural effusion, and pelvic examination will not be done because of lack of complaint localized to this region. A high index of suspicion of Meigs' syndrome should lead to pelvic examination and the demonstration of a tumor.

The differential diagnosis should include the consideration of all the diseases which will produce abdominal fluid and pleural effusion. The diagnosis of malignant pelvic tumors with metastasis to the pleural cavity is the most frequent pitfall in these cases. Particularly where a diagnosis of abdominal tumor has been made sometime before, the sudden appearance of ascites and pleural effusion has been considered *prima facie* evidence of malignancy; yet complete cure of Meigs' syndrome is reported in a case where previously an abdominal

tumor had been known to exist for 8 years.<sup>27</sup> Heart disease, with a rapidly failing heart and accumulation of fluid in serous cavities and tissues, must be ruled out. Peripheral edema and tissue edema is rarely if ever encountered in Meigs' syndrome, however, the coëxistence of these conditions in the elderly female must be borne in mind. Cirrhosis of the liver and tuberculosis must also be considered. In the former, a palpable liver or spleen or both will serve for diagnosis, while in the latter the demonstration of the tubercle bacillus or the finding of a lung lesion on Roentgen ray after paracentesis will clinch the diagnosis.

Laboratory tests on the blood, urine, or ascitic or pleural fluid will not be of any specific aid in the diagnosis of Meigs' syndrome except to exclude other conditions. The ascitic or pleural fluid itself in Meigs' syndrome appears to have no special properties except those expected of a transudate.

The prognosis in Meigs' syndrome is excellent if the ovarian tumor is removed. With the ablation of the tumor, the patient ceases to form abdominal fluid, the pleural cavity clears, and recurrence does not take place. The general health, weight, and entire clinical course improves. Even those patients who seem to appear exhausted and cachectic and have traveled from doctor to doctor or clinic to clinic receiving numerous abdominal and thoracic paracentesis—with rapid reaccumulations of the fluid and continued dire prognosis—do miraculously well after operation. This has happened in spite of the fact that in several of the reported cases the patients were over 70 years of age.

Meigs' syndrome has been elevated to a classical clinical entity, as attested by an increasing literature on the subject. Its importance lies in the fact that it is a benign disease which is easily and permanently cured by laparotomy and removal of the offending tumor. The syndrome is fatal only when misdiagnosed, which places the responsibility of the outcome directly on the shoulders of the medical profession. It is most interesting to note that whenever this subject comes up at a medical meeting,<sup>10,22</sup> at least several of the attending physicians do not fail to recall cases of Meigs' syndrome which they have seen. Some of these cases have resulted fatally, and autopsy has revealed typical cases which could have been saved by early operation. Of the cases that have survived, all the physicians have expressed delight, surprise, and a distinct sensation of relief at the unexpected outcome and smooth recovery of a patient that had been doomed by the pre-operative diagnosis of abdominal malignancy with metastasis.

It thus behooves general practitioners, internal medical men, and surgeons to keep this entity in mind when dealing with females who present themselves with chest fluid as a predominant symptom. Pelvic examinations should be done in all these cases and ovarian tumors ruled out by the most careful and scrupulous examination. When the examination of the pleural or ascitic fluid reveals no specific disease surgeons should be encouraged to perform exploratory lapar-

otomy even when in their clinical judgment malignant disease with metastasis seems obvious. This should be done regardless of the apparently exhausted and cachectic condition of the patient.

**Summary.** 1. Meigs' syndrome may be caused by other benign pelvic tumors than the ovarian fibroma originally described by Meigs.

2. A case of Meigs' syndrome with recovery is reported due to a massive multilocular cystadenoma of the ovary. This is a distinct rarity, as it is the second case to be noted in the literature.

3. Meigs' syndrome is probably not as uncommon as the literature would indicate. The increase in reported cases is most likely due to the increased recognition of the condition rather than to an increase in incidence.

4. Both internists and surgeons should be made more aware of this condition as the outcome of the undiagnosed case is fatal, as compared to the 100% recovery in the properly treated case.

5. More of these cases should be reported as they occur and a registry opened for their tabulation, so that adequate recognition can be given to this syndrome and a true basis of incidence established.

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# A RELATION BETWEEN CELL-PACK (HEMATOCRIT) VOLUMES AND LYMPHOCYTE COUNTS\*

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IN the course of a study of factors affecting the health and efficiency of medical students, a set of numerical measurements or scores were obtained for each of 37 students who volunteered.<sup>6</sup>

One consequence of this was the disclosure of an unexpected relationship, which is the subject of this paper, between cell-pack volumes (hematocrit readings) and the percentage of lymphocytes found in the differential blood count.

The reason for including the cell-pack volume in the study was that a run-down physical condition might reasonably be expected to be associated statistically with anemia, and so with a lowering of the ratio of total corpuscular volume to plasma volume. The reasons for doing the differential counts were: (1) the generally accepted principle that there is likely to be a lymphocytosis in chronic infections and in the aftermath of acute infections,<sup>7</sup> and (2) the impression of physicians that there is a tendency to lymphocytosis in men who are overworking.<sup>4</sup>

TABLE 1.—RELATION OF THE NUMBER OF LYMPHOCYTES TO CELL-PACK VOLUME

Lymphocytes	39, 40	41, 42	43, 44	45, 46	47, 48	49, 50	51, 52	Totals
15 to 19	..	..	..	..	..	..	1	1
20 to 24	..	..	1	3	..	1	..	5
25 to 29	..	..	2	1	1	3	3	10
30 to 34	..	1	1	4	..	..	..	6
35 to 39	..	1	..	2	2	..	..	5
40 to 44	..	..	1	1	1	1	..	4
45 to 49	1	..	1	..	..	..	..	2
50 to 54	..	1	..	..	..	..	..	1
55 to 59	..	..	..	1	..	..	..	1
	1	3	6	12	4	5	4	35*

Correlation coefficient  $r = -0.428 \pm 0.093$ .

\* Data incomplete for 2 of the 37 subjects.

This paper will also include passing mention of the body weight and the sedimentation rate. The sedimentation rates, cell-packs, and differential counts were all done according to methods that have been in constant use in this laboratory<sup>5</sup> for some years. This latter fact is significant because the phenomenon we wish to report, having first

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caught our attention in the study of the 37 medical students, was then found also to be demonstrable in the records of our dispensary patients.

Table 1 shows that a high lymphocyte percentage was associated with a low cell-pack volume. A consideration of the probable error showed that a correlation coefficient of  $-0.43$  would arise by chance in a sample of 35 subjects about 3 times in 1000.

This result proved to be quite consistent with other conclusions drawn from the study of the 37 students. To illustrate, six of the possible correlations are given in Table 2.

TABLE 2.—COEFFICIENTS OF CORRELATION AMONG BODY WEIGHT, SEDIMENTATION RATE, CELL-PACK VOLUME, AND PERCENTAGE OF LYMPHOCYTES

	Body weight	Sedimentation rate	Cell-pack volume
Percentage of lymphocytes . . . . .	$-0.26$	$+0.22$	$-0.43$
Cell-pack volume . . . . .	$+0.19$	$-0.29$	
Sedimentation rate . . . . .	$-0.50$		

This table indicates, for instance, that a negative correlation ( $-0.26$ ) was found between lymphocyte percentage and body weight. For 37 pairs of data, coefficients of  $\pm 0.30$  could arise by chance oftener than 5 times in 100; hence only the coefficients  $-0.43$  and  $-0.50$  in the table are significant by the conventional standard. But it is to be noted that the algebraic signs of the coefficients are in agreement with the assumption that low body weight, low cell-pack, high lymphocyte percentage, and high sedimentation rate are associated with the run-down state and hence with each other. When high is associated with high (or low with low), the sign of the correlation coefficient should be positive; when high is associated with low, the coefficient should be negative. Accordingly, the signs should be these:

	Body weight	Sedimentation rate	Cell-pack volume
Lymphocyte percentage . . . . .	$-$	$+$	$-$
Cell-pack volume . . . . .	$+$	$-$	
Sedimentation rate . . . . .	$-$		

The agreement between theory and results is seen to be perfect.

TABLE 3.—RELATION OF NUMBER OF LYMPHOCYTES TO HEMATOCRIT VALUES

Lymphocytes	Hematocrit														Totals
	9-11	12-14	15-17	18-20	21-23	24-26	27-29	30-32	33-35	36-38	39-41	42-44	45-47	48-50	
5-9 . . . . .							1	1	1						4
10-14 . . . . .							1	1							6
15-19 . . . . .				1			2	1				2	1		7
20-24 . . . . .	1			1	1	2	1	1	1	1		1	1		25
25-29 . . . . .				1	1	1	1	1	5	5		2	4		20
30-34 . . . . .				2	1	2	2	4	2	2	5	1	2		26
35-39 . . . . .		1		1	1	2	2	3	3	3	4	5	3		29
40-44 . . . . .		1		2	1	1	2	2	4	3	2	3	3		19
45-49 . . . . .			1		1		3	1	1	1	3	1			11
50-54 . . . . .					2		3	1	1	2					6
55-59 . . . . .					2	1		1		2					6
60-64 . . . . .		1						1				1			2
65-69 . . . . .						1				1					2
70-74 . . . . .											1				2
75-79 . . . . .															0
80-84 . . . . .							1								0
	1	3	1	7	9	10	16	17	17	21	20	16	14	8	160

Correlation coefficient  $r = -0.192 \pm 0.052$ .



Nevertheless, a study was made of the hematologic records of dispensary patients back to and including the year 1936. Records were found for 160 patients each of whom had had cell-pack determinations and differential counts done on the same day. The correlation table obtained by distributing these results showed some interesting features.

The over-all correlation coefficient for this table is seen to be  $-0.191 \pm 0.052$ , and is significant. It is lower than that given by Table 1; this is evidently connected with the fact that the cell-pack figures for the dispensary patients extend far down below the normal range, where the relation to the lymphocyte percentage is seen to become much vaguer. If one arbitrarily takes as normal the range seen for medical students in Table 1, and takes only the data for the 59 patients whose cell-pack volumes were between 39 and 50, one obtains  $r = -0.33$ .

**Discussion.** The negative correlation here found between cell-pack volume and percentage of lymphocytes in the differential count is strongest in the normal range and very much weaker in the subnormal range. This suggests the question whether some reciprocating mechanism may be at work in the normal body, operating in such a way that lymphocyte production would be depressed whenever erythrocyte production is temporarily more active. It is evident that a mere dilution of the blood by increasing its plasma content could not change the proportions among the colorless corpuscles in the differential count.

In favor of the assumption of a reciprocal relation between lymphocyte production and erythrocyte production is the finding by Kracke<sup>1</sup> that there is an increase in the absolute numbers of lymphocytes in the blood of many children with profound hypochromic anemia because of malnutrition.

On the other hand, the phenomenon seen in our own data could be explained on the assumption that from time to time, in the normal body, there is an accelerated discharge of lymph from the lymphatic ducts into the veins. Evidence obtained by Ehrlich and Lazarus<sup>3</sup> and by Rous,<sup>8</sup> indicating that lymphocytosis can be the result of this simple mechanical process, is quoted by Drinker and Yoffey.<sup>2</sup> These authors also point out that this assumption explains only moderate and transient degrees of lymphocytosis, of the sort that would constitute an immediate response of a normal body to some special stimulus like exercise or the administration of a drug. This would be in agreement with our finding that the correlation between lymphocytosis and blood dilution (in the sense of low cell-pack volumes) is best in the normal range.

**Summary.** Cell-pack determinations in 35 medical students proved to have a significant negative correlation with the percentage of lymphocytes found in the differential count. The same correlation was found in results from 160 dispensary patients; it was strongest in the normal range and was obscured in the subnormal range.

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## PERNICIOUS ANEMIA AND CARCINOMA OF THE STOMACH— AUTOPSY STUDIES CONCERNING THEIR INTERRELATIONSHIP\*

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THE development of any two disease processes in the same individual leads quite naturally to conjectures concerning the nature of their relationship. When both conditions are manifested with considerable regularity, their common etiologic origin may in general be directly inferred. The apparently sporadic concurrence of two diseases in only a few of the many individuals afflicted with one or the other condition presents a much more subtle and difficult problem.

Interest in the coëxistence of pernicious anemia and carcinoma of the stomach dates back as far as 1876, when Quincke is said to have called attention to such a case. Since the turn of the century, increasing numbers of case reports have appeared. This trend appears to have been further accelerated since the advent of specific therapy for pernicious anemia. As a result, several investigations have been conducted to determine whether the two conditions are related etiologically or merely through chance. An even greater amount of attention has been directed to the mechanism upon which this relationship is based.

Further investigation of the problem seems justified inasmuch as certain practical implications of considerable significance may be inferred from such a causal relationship. Accurate analysis of the problem, however, is beset with a great many difficulties, which explains in part the fact that a final answer has not yet appeared.

At least 4 possible relationships become apparent upon a *a priori* consideration of the subject:

1. Pernicious anemia and carcinoma of the stomach may appear in the same individual solely through chance, in which case no etiologic interconnection may be inferred.

\* Based upon a thesis submitted to the Graduate Faculty of the University of Minnesota by the first-named author in partial fulfillment of the requirements for the degree of Master of Science.

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2. The two conditions may develop concurrently more often than can be explained by the laws of probability, in which case:

(a) Carcinoma of the stomach may cause pernicious anemia or a condition so closely simulating it as to defy differentiation.

(b) Pernicious anemia may cause the development of gastric malignancy.

(c) A factor common to both conditions may act as a precursor of each and serve to explain their coexistence.

Statistical treatment of the problem requires the accumulation of adequate and accurate data. It is at this point that some of the major difficulties involved become apparent. For many years, conclusive criteria for the diagnosis of pernicious anemia were lacking. The earlier investigators were therefore confronted with the dilemma of proving that true pernicious anemia was present in the cases studied. This diagnostic difficulty has been diminished to some extent by the elucidation of newer and more stringent criteria, but the diagnosis of pernicious anemia still requires a considerable amount of clinical and laboratory data of rather specialized nature. Many of the previous publications on this subject have suffered from a lack of data adequate to permit a clear-cut diagnosis in all cases.

Emphasis has long been laid upon the well-known fact that a macrocytic type of anemia which superficially resembles pernicious anemia may occur in patients with gastric cancer. As a result of this emphasis, there appears to be a widely held view that any macrocytic anemia encountered in association with a gastric malignancy is secondary to the neoplasm. Both clinicians and pathologists have therefore been prone to discard an initial diagnosis of pernicious anemia in favor of a secondary anemia in such cases. This appears to have occurred even in numerous instances in which the evidence of pernicious anemia has been entirely convincing. To date, no analysis of autopsy data pertinent to the problem has taken such diagnostic errors into consideration. The present study was undertaken in an attempt to elucidate further evidence concerning the relationship of pernicious anemia to carcinoma of the stomach by a review of autopsy material.

**Review of the Literature.** Extensive reviews of the published case reports and of other evidence bearing upon the problem have been presented by Cotti,<sup>8</sup> Washburn and Rozendaal,<sup>41</sup> and Jenner.<sup>20</sup> To avoid reduplication of effort, no exhaustive review has been attempted here. Among the many case reports of coexisting pernicious anemia and gastric carcinoma which have appeared in recent years are those of Nesler,<sup>29</sup> Bronstein,<sup>4</sup> and Hagyard.<sup>15</sup>

A series of publications based upon large numbers of cases of pernicious anemia has issued from the Mayo Clinic in the past 20 years. The results noted illustrate strikingly the apparent trend to an increasing coexistence of the two diseases. In 1923, Giffin and Bowler<sup>13</sup> noted only 1 gastric carcinoma and 4 other malignant neoplasms in a series of 628 patients with pernicious anemia. Conner and Birkeland<sup>7</sup> encountered 20 cases of coexistence of pernicious anemia and carcinoma of the stomach among 658 patients with the former disease seen in the period from 1925 to 1930. The next report was that of Washburn and

Rozendaal,<sup>41</sup> who found 11 more such cases in the ensuing 3-year period. Recently, Doehring and Eusterman<sup>9</sup> reported on 1014 cases studied from 1935 to 1939, of which 17 also had carcinoma of the stomach. They stated that a total of 40 such cases has been noted at the Mayo Clinic since 1917, in 26 of which the diagnosis of pernicious anemia was established before symptoms referable to the gastric neoplasm became apparent.

Multiple cases of coexisting pernicious anemia and gastric carcinoma have been reported by Jenner,<sup>20</sup> Fitz-Hugh,<sup>12</sup> Strandell,<sup>36</sup> Cotti,<sup>8</sup> Hurst,<sup>18</sup> Murphy and Howard,<sup>28</sup> Rigler,<sup>31</sup> and others. In many of these cases blood disease existed for many years before the malignant neoplasm supervened. Thus, a patient reported by Miller<sup>26</sup> gave evidence of pernicious anemia for 17 years prior to the development of a gastric carcinoma. Pernicious anemia was present for 4 and 6 years, respectively, in the 2 cases reported by Cotti,<sup>8</sup> before symptoms of the gastric tumor were noted. Doehring and Eusterman<sup>9</sup> found in their series that the average interval between the onset of symptoms of pernicious anemia and those of carcinoma of the stomach, in cases where such a determination could be made, was 8.7 years.

The association of pernicious anemia with gastric neoplasms is not limited to carcinoma. Adenomatous polyps have also been encountered frequently in patients with Addisonian anemia. Washburn and Rozendaal<sup>41</sup> noted 8 such cases, and Doehring and Eusterman<sup>9</sup> later added 4 more. Six cases were observed by Velde<sup>40</sup> in a series of 42 patients with pernicious anemia, an incidence of 14%. In a control series of 1271 patients with a variety of other diseases, the incidence of gastric polyps was only 0.71%. Haring<sup>16</sup> reported 7 cases of coexistent gastric polyps and pernicious anemia. Three such cases were encountered by Schindler and Serby<sup>34</sup> in a gastroscopic study of 23 patients with pernicious anemia. Numerous other cases have been described; however, no attempt has been made to compile all such instances.

The coexistence of gastric polyps and pernicious anemia is particularly important in view of the apparently precancerous nature of such polyps. Miller, Eliason, and Wright<sup>27</sup> in 1930 collected 24 cases in which adenomatous polyps had progressed to frank gastric carcinoma and added 8 cases personally observed in a series of 23 gastric resections for polyps. The incidence of malignant degeneration in their cases was 35%. Stewart<sup>35</sup> found carcinoma associated with 13 of 47 gastric polyps. Nine of the 50 polyps noted by Lawrence<sup>23</sup> showed histologic evidence of malignancy. McRoberts<sup>25</sup> carefully studied 5 cases of gastric polyps and found histologic evidence of "carcinoma *in situ*" in 4 of them. Similar evidence of malignant change was found by Haring<sup>16</sup> in 4 of his 7 cases. Rigler and Ericksen<sup>32</sup> found malignant degeneration in 4 of 25 polyps detected roentgenologically, and in 4 of 31 encountered in studies of autopsy material. In 7 instances noted by Benedict and Allen<sup>1</sup> among a series of 17 polyps, malignant features became manifest upon histologic study of the resected tumor, or the patients later died of gastric carcinoma. Thus, it would appear

that the demonstration of gastric polyps in association with pernicious anemia has almost the same significance as the demonstration of carcinoma *per se*.

In addition to the case reports enumerated above, there have been a few systematic and thorough investigations based upon both autopsy and clinical material. Rambach<sup>30</sup> found 641 cases of gastric carcinoma and 50 cases of pernicious anemia in a series of 11,849 postmortem examinations. On the basis of chance alone, the incidence of coëxistence of the two diseases is the product of their respective incidences, or approximately 2.4 cases for the entire series. Actually, 11 cases of combined pernicious anemia and gastric carcinoma were encountered which represents a statistically significant deviation. In a small series of 22 cases of pernicious anemia studied by Brandes,<sup>3</sup> 4 carcinomas of the stomach were observed at autopsy, an incidence of 18%. Jenner<sup>20</sup> reviewed the autopsy findings in 76 patients with pernicious anemia, and noted 5 gastric carcinomas and 4 benign gastric tumors. Only 1 other malignant tumor was observed, which arose in the uterus. Among a total of 18,200 postmortem examinations recorded between 1897 and 1933, Madeleine Brown<sup>5</sup> found a total of 151 cases of pernicious anemia, of which 12 (8%) had gastric polyps, and 1 additional case had a gastric carcinoma. The incidence of gastric polyps among the remaining autopsies was only 0.003% in her study. The control figure given must be in error, however, and the more generally accepted autopsy incidence of 0.5% may be used for comparison.

One of the most extensive clinical studies which has appeared is that of Jenner.<sup>20</sup> He found 8 cases of associated gastric carcinoma in a series of 181 patients with well-authenticated pernicious anemia. By applying the corrected mortality incidence of carcinoma of the stomach to the living population of the city of Amsterdam he arrived at the morbidity incidence for gastric cancer in various decades. Comparison of this incidence with that in his pernicious anemia patients revealed that the incidence of gastric neoplasms in the latter group was at least 12 times as high as that in the general population of corresponding age. Similarly, Van der Sande<sup>39</sup> developed morbidity statistics for gastric carcinoma, and calculated the expected incidence of coëxistence of the 2 disease processes. This was then compared with the actual incidence of association as reported in various earlier publications, and again the actual frequency was obviously far higher than that expected on a chance basis.

Cotti<sup>8</sup> presented a compilation of published cases of pernicious anemia associated with some form of malignant tumor. He found that among 107 cases of this type, the neoplasm was primary in the stomach in 93, or 86%. It is generally considered that gastric carcinoma represents about 30% of all malignant tumors coming to autopsy, and its relative incidence in living individuals is somewhat less than this value. The proportion of gastric malignancies encountered by Cotti is therefore far beyond that which would be expected upon a probability basis.

It is apparent, therefore, that evidence is available which is at

least strongly suggestive of an etiologic relationship between pernicious anemia and gastric carcinoma. We are not primarily concerned here with the mechanism of this relationship. Only a brief outline of the mass of evidence pertinent to this phase of the subject will therefore be considered.

A number of investigators have pointed out the tendency of patients with gastric carcinoma to develop anemia of macrocytic type, and have also considered this neoplasm a possible cause of true pernicious anemia. In the light of the classical work of Castle and his collaborators, this view was supported by the argument that destruction of the gastric mucosa by the tumor might lead to a loss of the "intrinsic factor," and could thus eventuate in pernicious anemia. However, attempts by a great number of other investigators to produce anemia in animals by the operative removal of the stomach and in some cases of portions of the small intestine as well have all led to failure. Similarly, very few patients among the great number annually subjected to gastrectomy ever develop true pernicious anemia. Thus, Doehring and Eusterman<sup>9</sup> report that follow-up examinations of 575 gastrectomized individuals yielded not a single case of pernicious anemia. Furthermore, the occurrence of pernicious anemia in patients with very small tumors which could scarcely destroy much of the gastric mucosa tends to refute this contention. It appears doubtful, therefore, that carcinoma of the stomach is a direct precursor of pernicious anemia.

The next possibility to be considered is that, conversely, pernicious anemia may be a precursor of gastric carcinoma. It is at once obvious that pernicious anemia *per se* can hardly be considered the main or the only cause of malignant gastric neoplasms, inasmuch as the latter occur far more frequently. However, there is almost no evidence to establish or refute the possibility that pernicious anemia may be only one, perhaps a very minor one, among several causes of carcinoma of the stomach. The literature of experimental cancer research is replete with examples of multiple causes of several varieties of cancer. It is therefore quite possible that the causes of gastric cancer are likewise multiple.

The final consideration is that a factor common to both conditions may be a precursor of both, or a concomitant of one and precursor of the other. Among the factors of this type which have been enumerated are gastritis, achlorhydria and achylia, constitutional and hereditary factors, and liver therapy for pernicious anemia.

Konjetzny<sup>22</sup> and others have been enthusiastic proponents of the thesis that chronic gastritis, particularly of the atrophic type, is a precancerous lesion. This view is based upon the frequent demonstration of gastritis and of proliferative mucosal changes in the vicinity of malignant gastric neoplasms. However, the recent careful studies of Guiss and Stewart<sup>14</sup> and of Hebbel<sup>17</sup> indicate that chronic gastritis occurs very commonly in individuals past middle age, and is no more frequently associated with gastric cancer than with malignancies primary elsewhere or with non-neoplastic diseases.

The corollary thesis, that gastritis is a cause of, or is associated with, pernicious anemia, was enunciated by Faber<sup>11</sup> and Hurst.<sup>19</sup> However, Magnus and Ungley<sup>24</sup> studied fresh gastric specimens of individuals dying of pernicious anemia and found no evidence whatsoever of inflammatory change. The only constant finding was atrophy of the mucosa in the fundus and corpus of the stomach. Moreover, it has been demonstrated gastroscopically that the apparent gastritis and atrophy noted in pernicious anemia patients may and often does disappear following adequate liver therapy.<sup>21</sup> Despite the disappearance of atrophic gastric changes in such patients, they may go on after a number of years to the development of gastric carcinoma, as in the cases of Dyke and Harvey.<sup>10</sup>

Haring<sup>16</sup> and others have suggested that achlorhydria and achylia gastrica represent a functional deficiency of the gastric mucosa, which may lead, in an attempt to compensate for the deficiency, to hyperplasia, proliferation, and finally to the development of neoplasms. This theory is somewhat analogous to the known proliferative overgrowth of the thyroid gland in the presence of iodine deficiency. However, the frequency of achlorhydria is so great in relation to the incidence of gastric carcinoma that it must be doubted whether it constitutes a direct cause of the malignant condition. Pending the appearance of further evidence pertinent to this question, the rôle of achlorhydria and achylia in gastric carcinogenesis remains in dispute.

Conner<sup>6</sup> effectively demonstrated the hereditary basis of achlorhydria in pernicious anemia patients. A number of other authorities have reported the occurrence of pernicious anemia in several members of the same family in one or more generations. The evidence for a hereditary and constitutional factor in the development of gastric carcinoma is likewise suggestive. Finally, the occurrence of one or both of these diseases in several members of a single family has been reported by others.<sup>2,33</sup> There is, therefore, some evidence, admittedly far from conclusive, to indicate that hereditary factors conditioning the development of both pernicious anemia and gastric carcinoma may be linked in some manner to explain the coëxistent occurrence of the two diseases in the same individual.

The final hypothesis requiring mention is that of Teuffl,<sup>37</sup> who suggested that the increased incidence of gastric carcinoma in pernicious anemia patients since the advent of liver therapy was due, not to the greater longevity of these patients, but to a carcinogenic effect of the therapeutic liver preparations. Despite our knowledge of the experimental production of skin and subcutaneous tumors in mice by local application of certain liver extracts, this hypothesis remains largely unsubstantiated.

**The Present Investigation.** *Material and Procedure.* This investigation is based upon a study of pertinent cases among a total of 43,021 consecutive autopsies recorded in the Department of Pathology of the University of Minnesota during the period from 1915 to 1943. Although all cases of pernicious anemia were supposedly recorded in the departmental index, it was felt that an unknown number of additional cases might have occurred in associa-

tion with gastric carcinoma and with other diseases in which the diagnosis of pernicious anemia was discarded or unrecognized at the time of the post-mortem examination.

Therefore the problem was approached in several ways in an attempt to obtain a reasonably correct incidence of the association of carcinoma of the stomach with pernicious anemia. The first series of cases included all autopsies in which pernicious anemia was listed among the postmortem diagnoses. After elimination of certain cases in which some evidence was available to refute the diagnosis of pernicious anemia, Series 1 was found to have a net total of 146 cases. These were then carefully studied for the incidence of benign and malignant gastric and other neoplasms.

Series 2 is comprised of all cases of gastric carcinoma occurring in the period studied. Of 1010 such cases, 694 were found to have clinical and laboratory data recorded in the autopsy protocols which were regarded as adequate to either exclude or clearly establish the diagnosis of pernicious anemia. A critical review of these data yielded a considerable number of additional cases of coexisting pernicious anemia which had not been encountered in the study of Series 1. With this preliminary evidence to support the hypothesis outlined above, concerning the inaccuracy of autopsy diagnoses of pernicious anemia, the next procedure was a parallel review of a large number of cases of another form of gastro-intestinal malignancy. Series 3 consisted of all cases of carcinoma of the colon, rectum, and cecum; of 775 cases, 509 had adequate clinical and laboratory data.

The finding of "occult" cases of pernicious anemia during a study of Series 2 and 3 suggested that perhaps additional cases were similarly unrecognized in association with other malignant conditions or with non-neoplastic diseases. The task of reviewing all autopsies in the entire series for the corrected total incidence of pernicious anemia would have been overwhelming. It was therefore decided to review critically all autopsies in individuals of a selected age group in certain sample years. The percentage of "occult" cases of pernicious anemia detected in these years could then be applied to the total number of individuals of the designated age group in the entire autopsy population to arrive at the total number of cases believed to have been unrecognized. Addition of this group to those already accepted as pernicious anemia would yield the corrected total incidence of pernicious anemia among individuals of roughly comparable age. This figure is necessary to compute the incidence of association of gastric carcinoma and as a basis for statistical analysis.

From this outline of procedure it becomes evident that the value of the entire investigation hinges upon the accuracy with which the diagnosis of pernicious anemia can be established by such a retrospective analysis of data available in autopsy protocols. The only procedure possible at autopsy which would be of any diagnostic value is a study of the bone marrow. Unfortunately this is impossible in most autopsies due to rapid postmortem autolytic changes. In addition, many cases of pernicious anemia die in remission, from some intercurrent complication, at a time when the bone marrow does not present a characteristic picture. The diagnosis, therefore, usually rests wholly upon data obtained during life; diagnostic procedures yielding questionable values cannot be repeated and there are often gaps in the information required for a clearcut diagnosis which can no longer be filled in.

In general, it may be stated that the diagnosis of pernicious anemia was excluded in all cases in which one or more clinical features incompatible with or rarely encountered in this disease were encountered. The diagnosis was accepted only in those cases presenting clear-cut data of characteristic nature; in rare instances cases with incomplete but otherwise acceptable data were included. All other cases with incomplete data were not considered as having pernicious anemia. The diagnostic criteria were adhered to with particular rigor in Series 2, composed of cases of gastric carcinoma.

*Results of the Investigation.* A total of 27 tumors was encountered among 146 cases of pernicious anemia constituting Series 1. Of these,



only 11 originated extra-gastrically. There were 9 cases of carcinoma and 7 with polyps of the stomach. In 1 case, multiple polyps were present. Six extra-gastric malignancies were noted, arising in the prostate in 3 cases, and in the kidney, breast, and urinary bladder in 1 case each. The 5 benign extra-gastric tumors originated in the uterus, sigmoid, appendix, and small intestine. In this incomplete study alone, gastric tumors of either benign or malignant nature constituted 60% of all observed neoplasms.

In addition to the 9 cases of coëxistent pernicious anemia and gastric carcinoma noted above, 27 cases of the former disease which had been discarded or not clearly recognized at autopsy were encountered in Series 2 among 694 cases of carcinoma of the stomach. Thus a total of 36 individuals had both diseases in this autopsy series. As stated in a preceding section, an additional number of cases may well have had pernicious anemia, but were not included as such because of incomplete data.

Similarly, the parallel study of Series 3, consisting of 509 cases of carcinoma of the colon, rectum, and cecum yielded 4 cases of previously unrecorded pernicious anemia. This also represents the total incidence of coëxistence of the 2 diseases, inasmuch as no cases were encountered in Series 1. Comparison with the incidence of pernicious anemia in cases of gastric carcinoma at once reveals the much higher frequency with which pernicious anemia is associated with gastric malignancies than with malignant tumors arising elsewhere in the gastro-intestinal tract. The incidence was 5.1% among 703 cases of gastric carcinoma and only 0.8% in 509 cases of carcinoma of the colon, rectum, and cecum.

All autopsy protocols of individuals 45 years of age or over were reviewed in the sample years 1920, 1930, and 1940 to obtain the percentage of unrecognized or discarded cases of pernicious anemia in these years. In many instances, the autopsies concerned individuals who were found dead or who died suddenly as a result of trauma or other cause. Clinical data in such cases were either completely lacking or grossly inadequate to exclude the possibility that pernicious anemia might have been present during life. These cases were therefore omitted from study.

In the year 1920, there were only 38 cases with adequate data for study among 180 individuals of proper age. No instances of unrecognized or discarded pernicious anemia were encountered in this small group. In 1930, there were 942 autopsies on individuals of the selected age group, of which 384 had adequate clinical data to establish or refute the diagnosis of pernicious anemia. Only 2 cases of "occult" pernicious anemia were discovered in this year, both in individuals dying of non-neoplastic diseases. The year 1940 yielded 5 more cases of "occult" pernicious anemia among 917 autopsies acceptable for analysis. Four of these 5 occurred in association with non-neoplastic disease. Thus a total of 7 cases of pernicious anemia was unearthed from a study of 1339 individual autopsy protocols, an incidence of 0.5%.

Of the individuals in these 3 sample years 54% were 45 years of age or over. Applying this percentage to the entire autopsy period, we find that a total of 23,231 autopsies were performed upon individuals of the designated age range. The number of "occult" cases of pernicious anemia for the entire period is therefore 0.5% of this total, or 116 cases. An additional 31 cases were noted in the study of Series 2 and 3, bringing the total of unrecognized cases to 147. To these must be added the 146 known cases from Series 1; the estimated total in the entire autopsy series, arrived at in this manner, is 293 cases of pernicious anemia, limited almost entirely to individuals 45 years of age or over.

There were 36 cases of known association of pernicious anemia and carcinoma of the stomach among the 293 cases of pernicious anemia believed to have occurred. This represents an incidence of gastric carcinoma, among all cases of pernicious anemia coming to autopsy, of 12.3%. The incidence of gastric carcinoma among all other autopsied individuals of comparable age was slightly less than 4%, less than one-third of that found in individuals with pernicious anemia.

Statistically, the incidence of expected coëxistence is the product of the respective incidences of the two diseases. Thus, on the basis of chance alone, 5 individuals per 10,000, or a total of 12 cases among the 23,231 cases of the selected age range, would be expected to exhibit both conditions. The actually observed number of cases was 36, and the difference between the observed and expected incidence was therefore 24 cases. The standard error was found to be 3.41 and the ratio of the observed difference to the standard error is 7.40. The probability that the observed result is due merely to chance was found to be less than 1 billion.\* This constitutes conclusive statistical evidence of an etiologic relationship between carcinoma of the stomach and pernicious anemia.

**Discussion.** The establishment of an etiologic relationship between pernicious anemia and carcinoma of the stomach has many important implications. It directs attention to the factors underlying the occurrence of carcinoma of the stomach as outlined above. Further investigation of the hereditary or constitutional factors involved is clearly indicated. Secondly, the knowledge that individuals with pernicious anemia are prone to develop carcinoma of the stomach indicates the necessity for frequent examination of such patients in order to make the diagnosis at as early a stage as possible. A study of the utility of the routine Roentgen examination, at semi-annual intervals, of all individuals with pernicious anemia has been reported elsewhere.<sup>33</sup> Finally, the frequent occurrence of carcinoma of the stomach in a select, readily chosen group of individuals, should permit an adequate study of the early signs and symptoms and of the development and course of carcinoma of the stomach from its incipency.

**Summary and Conclusions.** 1. Data in the literature indicate the probability that pernicious anemia and carcinoma of the stomach occur frequently in the same individual.

\* We are greatly indebted to Prof. A. E. Treloar of the Division of Biostatistics for aid with the statistical analysis of the results of this investigation.

2. The theories as to the reasons for the coincidence of the 2 diseases are reviewed.

3. A study of 23,231 autopsies on individuals 45 years of age or over is presented.

4. In 293 cases of pernicious anemia, found in this series, 36 also had carcinoma of the stomach, an incidence of 12.3%, which is over three times as great as the incidence in the remaining autopsy population of the same age.

5. Unequivocally the statistics indicate that there is an etiologic relationship between pernicious anemia and carcinoma of the stomach.

6. Patients with pernicious anemia should therefore be examined frequently to detect the onset of carcinoma of the stomach.

We are indebted to Drs. C. J. Watson and Macnider Wetherby for many valuable suggestions and to Dr. E. T. Bell for the privilege of studying the autopsy material from his department.

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# CORONARY INSUFFICIENCY, REVEALED BY ECTOPIC NODAL AND VENTRICULAR BEATS IN THE PRESENCE OF LEFT BUNDLE BRANCH BLOCK

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BECAUSE the ECG signs of recent myocardial infarct are often obscured by intraventricular block, Dressler's recently published report<sup>1</sup> that myocardial infarct was indicated by 2 ventricular premature beats, although the regular beats, in the presence of left bundle branch block, failed to display significant changes, is important. In this report a similar case is presented in which the electrocardiographic material is even more complete, because more premature beats and more tracings are available. The regular beats fail to give definite evidence of myocardial infarction in the presence of left bundle branch block.

**Case Report.** The patient, a white male, was 75 years of age. The past medical history was essentially negative except for an episode, 10 years ago, of pain "between shoulder blades in the middle of back" similar to that of the present illness. Pain was of gradual onset, lasted for a few days, and was relieved by heat and rest. He returned to his usual work without any symptoms related to his cardiovascular system. About 2 weeks before hospitalization (3/20/44), following moderate exertion, patient experienced an intense pain localized over the fourth dorsal vertebra posteriorly. At first it was relieved by heat. Within 10 hours the pain became agonizing and radiated down the left arm to the little finger and around his neck and both clavicles. Nausea was slight, weakness and sweating were moderate. Dyspnea was not present. These symptoms were only partially controlled by heavy narcotic sedation, varied in intensity for about 12 days climaxing in a status anginosus on admission to the hospital. Physical examination on admission to the hospital revealed a well-nourished male with only a moderate degree of arteriosclerosis as evidenced by his fundi and slight beading of his peripheral vessels. There were no physical signs of shock; color good; very little dyspnea. Heart sounds were distant, no murmurs, no friction rubs detected. Blood pressure right arm 190/118, left arm 148/90. Lungs were clear. Abdomen negative. Pulse 98 per minute, irregular. Clinical course: During the first 72 hours patient was treated with the usual narcotic and barbiturate sedation, intravenous papaverine and oxygen. His pain gradually subsided. Temperature varied from 99.4° to 100.4° F. However, his pulse became very irregular. Quinidine was started 72 hours after admission. Twelve hours later patient had an episode of syncope, sweating, pulse 48 per minute, blood pressure 100/60. Apex tones were very distant. Over a period of 6 hours the blood pressure returned to right arm 136/70, left arm 116/62. The blood pressure remained at these levels throughout the remainder of his illness. Quinidine therapy was continued at 20 gr. daily. After 40 days the patient was discharged from the hospital ambulatory and symptom-free. Temperature

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remained normal after the 8th day of admission to hospital. Kline was negative. Except for a trace of albumin on admission, urine was negative. R.B.C. 4,460,000, hemoglobin 15.5 gm., W.B.C. 20,700 on admission to 16,750 on 4th day, non-segmented polys varied from 17 to 26% the first 4 days. Sedimentation rates: 3/23/44, 52% after 60 minutes (3rd day of admission); 3/30/44, 59% after 60 minutes (10th day of admission); 4/25/44, 90% after 60 minutes (35th day of admission).

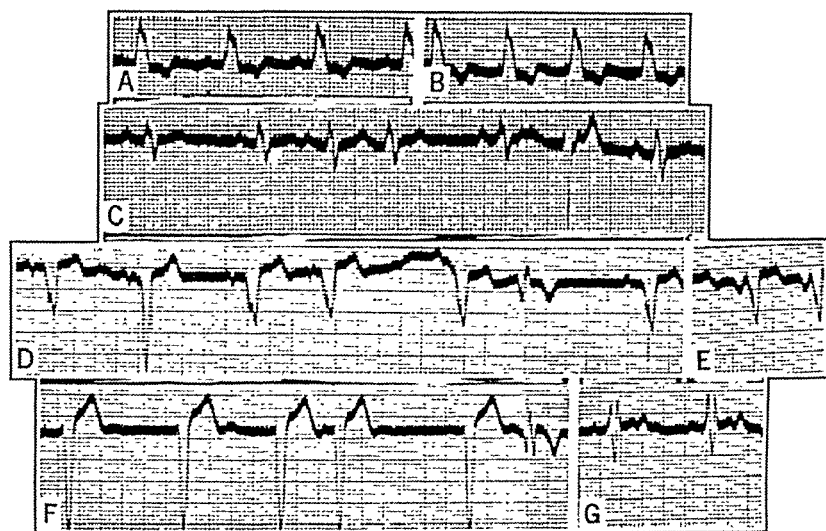


FIG. 1.—A and B, Lead 1; C, Lead 2; D and E, Lead 3; F, Lead CF<sub>2</sub>; G, Lead CF<sub>4</sub>. D and F show a premature ventricular beat with coronary insufficiency configuration (observed in the regular beats by left bundle branch block).

**Description of Electrocardiograms.** The first tracing was taken 24 hours after admission to the hospital, *i. e.*, about 2 weeks after the beginning of the attack. The ECG shows left bundle branch block (QRS interval 0.14 second) and a peculiar type of arrhythmia in Lead 1. Runs of sinus rhythm of lower frequency (Fig. 1a, Lead 1 [4 beats]) change with a faster nodal rhythm (Fig. 1b, Lead 1). In Lead 2 (Fig. 1c) QRS is about equiphasic, the third and fourth beat premature auricular (P coinciding with T), the sixth probably premature ventricular with a much taller and peaked T wave. No preceding P wave is visible, and the fact that the pause is not fully compensatory might be due to the existing sinus arrhythmia. In Lead 3 (Fig. 1d) the QRS interval in the regular beats is 0.12 second; the P wave is diphasic in the first 3 beats, but the second QRS complex is much larger and narrower (QRS = 0.1 second). The sixth beat is probably premature ventricular with a prominent notched Q wave of 4 mm. and an inverted T wave of -3.5 mm. The QRS interval is 0.12 second. It is noteworthy that this beat occurs after an excessively long R-R interval of 1.23 second. This beat is followed by a positive P wave. At the end of this lead there is a run of 12 faster, regular, nodal beats with inverted P wave, 2 of them shown in Figure 1e, obviously from a different focus than in Lead 1, because of the longer P-R interval. In Lead CF<sub>2</sub>, the first 3 beats of Figure 1f show irregular sinus rhythm,

the fourth beat is premature, probably nodal, followed by a compensatory pause; the last beat of Figure 1f is a premature ventricular beat (QRS W-shaped) with a large Q wave (4.5 mm.) and an inverted T of 4.5 mm. This premature beat is preceded by an R-R interval of 1.24 second. The same episode was repeated at the end of Lead CF<sub>2</sub>. No premature ventricular beats occurred in Lead CF<sub>4</sub> (Fig. 1g). Another ECG was taken after 24 hours. Figure 2a shows Lead 1. The second, third, sixth and seventh beats are the regular beats, initiated by a P wave with a P-R interval of 0.16 second and a QRS interval of 0.12 second. Blocked P waves are seen after the third, sixth and seventh beats. The first, fourth, fifth and ninth beats are preceded by

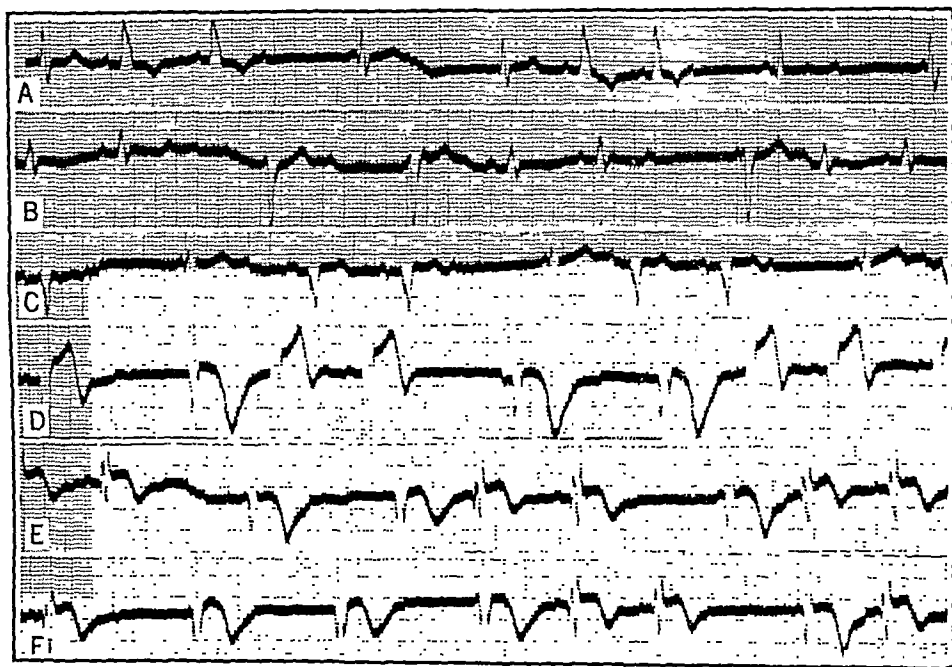


FIG. 2.—A, Lead 1; B, Lead 2; C, Lead 3; D, Lead CF<sub>2</sub>; E and F, Lead CF<sub>4</sub>. Ectopic beats in all leads (nodal or ventricular escape), most with shorter QRS interval than the regular beats with left bundle branch block. In Leads CF<sub>2</sub> and CF<sub>4</sub>, the ectopic beats (2 different types in Lead CF<sub>4</sub>) reveal the pattern of coronary insufficiency (increase of Q and inverted T compared with Figure 1). For further details see text.

a P wave with short P-R interval (0.06 second), therefore of nodal origin, with aberrant ventricular conduction resulting in an equiphasic QRS complex with a QRS interval of 0.1 second. The eighth beat is preceded by a P-R interval of 0.13 second; the QRS is up and of normal contour (QRS = 0.08 second). All following 16 beats of Lead 1 resemble the regular beats of Figure 2a; they are not included in Figure 2. The first 2 and the last 3 beats of Figure 2b show the regular sinus beats of Lead 2; blocked P waves occur after the second, third and sixth beats; the third, fourth and seventh beats are ectopic, the seventh beat obviously nodal, the others probably nodal because of the similar contour with beat 7. All 3 ectopic beats occur after a blocked P wave and are probably due to nodal escape. The same mechanism can be ob-

served also in Lead 3 (Fig. 2*c*) after the first, fourth and seventh beat. The regular beats of Lead CF<sub>2</sub> show a downward QRS deflection. Six ectopic beats were observed in this lead, all with a large Q wave of 8 mm. and a tremendous inverted T wave. Figure 2*d* shows 3 of these beats. None is followed by a compensatory pause, but the interval to the preceding QRS is excessively long (1.40, 1.40, 1.42, 1.42, 1.43, 1.40 seconds). They are due to escape mechanism, possibly ventricular. A notching at the end of the preceding T wave (marked by a dot) is probably a blocked P wave. The QRS interval of the regular beats is 0.12 to 0.13 second, that of the ectopic beats is 0.10, 0.08, 0.11, 0.10, 0.11 and 0.13 second; except the last one, there is a tendency to shorter QRS intervals. In Lead CF<sub>4</sub> (Fig. 2*e*) the regular beats show poly-

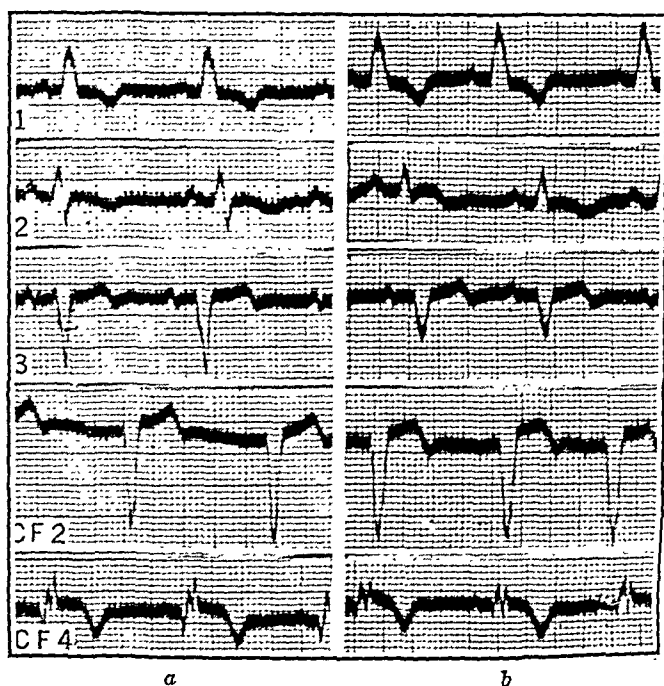


FIG. 3.—*a*, ECG after 10 days; *b*, after 1 month.

phasic QRS, with a small Q wave, S-T elevation and diphasic T wave. Eight ectopic beats were observed in this lead of 2 different types: (1) diphasic of Q-R type, with a large Q wave of about 6 mm. and an inverted peaked T wave of large amplitude (9 mm.); (2) triphasic W-shaped QRS with a Q and an R wave of about 4 mm., and an inverted T wave of 6 to 7 mm. amplitude. Figure 2*e* shows 3 ectopic beats, the first and third ectopic beat of Type 1, the second ectopic beat of Type 2; the other beats are the regular sinus beats. Figure 2*f* shows, after a regular beat, 3 consecutive beats of Type 2 and, the second last, of Type 1. The QRS interval of the regular beats is 0.12 to 0.13 second, that of the ectopic beats Type 1 is 0.09 to 0.10 second, of Type 2, 0.12 second. The Type 1 ectopic beats are preceded by a P wave with

short P-R interval, while only 1 of 3 ectopic beats of Type 2 is preceded by a diphasic P wave with short P-R interval (second beat, Fig. 2f). The R-R interval between the ectopic beats and the preceding beat is excessively long (about 1.40 second). The mechanism for the ectopic beats Type 1 is nodal escape, and for Type 2 nodal or ventricular escape. Blocked P waves are marked with a dot. Further tracings were taken after 3 days, 10 days, 15 days, 1 month and 2 months. Figure 3 shows the tracings taken after 10 days and 1 month later (3a and 3b). No further ectopic beats could be observed. The evolution of infarct is largely obscured by the left bundle branch block. Noteworthy is the Q wave in Lead CF<sub>4</sub>, associated with a sharply inverted T wave.

**Discussion.** We are not in a position to prove by autopsy that an infarction has occurred, since the patient recovered. The ectopic beats with Q waves and T inversion in Leads 3 and CF<sub>2</sub> of the first electrocardiogram (Fig. 1) and in the chest leads of the second one (Fig. 2) reveal a type of acute coronary insufficiency. The increasing T inversion in the ectopic beats of the second ECG, 24 hours after the first one, is obviously faster than it usually occurs in the evolution of myocardial infarct. The further development is obscured by the left bundle branch block, no further ectopic beats could be observed in the later electrocardiograms. However, the prominent Q wave in Lead CF<sub>4</sub>, associated with a sharply inverted T wave (Fig. 3) a few weeks after the attack, is suspicious of infarct, since Q waves in the chest leads of uncomplicated left bundle branch block are rare.<sup>5</sup> The clinical picture was compatible with that of coronary occlusion. Therefore, we think that a myocardial infarction of the septum probably occurred. In any case, the ectopic beats indicate an acute coronary episode, which is not revealed in the regular beats. Dressler<sup>1</sup> offers two explanations for a similar phenomenon in his case: (a) occasionally, premature ventricular beats may originate from a focus so located that the excitation wave activates the two ventricles which, in the presence of intraventricular block, are activated one after another in approximately normal sequence;<sup>4</sup> (b) when, in left bundle branch block, premature beats originate in the left ventricle late in diastole at the time when the normal sinus excitation is due in the ventricles, the opposed effects of the dextrocardiogram (due to the normal excitation) and of the levocardio-gram (due to the premature excitation) may produce an approximately normal ventricular complex.<sup>6</sup> The latter possibility could be ruled out in Dressler's case. One would expect in both mechanisms (a or b) a shorter QRS interval in the premature beats, while in Dressler's case the QRS interval is about the same in the regular and in the premature beats. The ectopic beats of the second electrocardiogram (Fig. 2), especially in Lead 1 (Fig. 2a) and Lead 3 (Fig. 2c), have a much smaller QRS interval than the regular beats; in fact, in most of these beats the QRS interval is within normal limits with a normal QRS contour; this is especially true for the eighth beat in Figure 2a. Many of the ectopic beats are preceded by a short P-R interval, so that they are of nodal origin. This excludes both mechanisms a and b. Theo-



retically, a mechanism similar to *b* could be assumed, in that a nodal impulse may coincide with a premature beat in the left ventricle. It is not probable, however, that this would occur so frequently.

We suggest another explanation. The ectopic beats in the second tracing (Fig. 2) are due to an escape mechanism, mostly of nodal origin. The interval to the preceding QRS is always excessively long, mostly due to blocked P waves. Obviously, the disturbance of conduction, resulting in left bundle branch block, is functional. If the heart rate is within normal range, the delayed refractory period of the left bundle branch produces intraventricular block. If the heart rate is very slow, the recovery of the left bundle branch is more complete, so that the next following beat shows a much shorter QRS interval with a more normal QRS contour. This mechanism of functional intraventricular block is known.<sup>2,3</sup> The variation of the contour in several ectopic beats might be explained by a different site of impulse formation; the P-R intervals vary somewhat; no P waves are discernible in several ectopic beats. In Figure 2 the presence of a type of coronary insufficiency is shown only in the ectopic beats of the chest leads and not in the limb leads. This phenomenon is not rare in anterior wall infarction, and the same explanation holds obviously for the ectopic beats in our case as for the regular beats in other cases. However, in the first tracing, one ectopic beat in Lead 3 (Fig. 1c) shows the contour of coronary insufficiency. The fact that the ectopic beats in Lead 3 of the second electrocardiogram do not reveal these features, is possibly due to partial recovery of this particular lesion. The appearance of the infarct or coronary insufficiency pattern only in the ectopic beats, is obviously explained by the more normal spread of the impulse through the ventricles. The QRS interval of the ectopic beats including those with the infarct pattern in Lead CF<sub>2</sub> and of Type 1 in Lead CF<sub>4</sub> is shorter than in the regular beats. The different shape of the Type 2 ectopic beats is obviously due to a different focus of impulse formation. Type 2 also shows the contour of coronary insufficiency (deep Q and T inversion), but the QRS interval is about the same as in the regular beats. Since they are preceded by a long R-R interval, sufficient to restore the conduction time of the left bundle branch, it could be possible that the prolonged QRS interval in these beats (Type 2) has nothing to do with the original left bundle branch block of the regular beats, but is due to the site of impulse formation, which is obviously lower in Type 2 than in Type 1. Obviously, the mechanism of the phenomenon in the first electrocardiogram (Fig. 1) is different. Here no P waves are discernible, and the QRS interval is not shorter than that of the regular beats. It is possible that they are of ventricular origin, but the broad QRS interval is not easily compatible with mechanism *a*. No escape mechanism is involved, the beats are undoubtedly premature. While we cannot offer a satisfactory explanation for the phenomenon in the first electrocardiogram (Fig. 1), we wish to call attention to a fact which obviously is of importance. The interval between the preceding QRS and both premature beats in Lead CF<sub>2</sub>, which show the phenomenon, is short (0.6 second), but the

R-R interval between the last 2 beats immediately before the premature beat is excessively long (1.24 seconds), longer than any other R-R intervals, and due to a premature nodal beat (third beat before the premature ventricular beat) with compensatory pause. Obviously, this combination was necessary to produce the phenomenon. In Lead 3 the same sequence: premature nodal beat, compensatory pause (R-R interval 1.24 seconds), premature ventricular beat with coronary insufficiency pattern, occurs as in Lead CF<sub>2</sub>. A certain proof for this assumption is an ectopic nodal beat in the same lead (third beat, Fig. 1*d*), with smaller QRS interval, normal QRS contour and without the coronary insufficiency pattern. The R-R interval of the preceding regular beats is not prolonged (0.96 second).

**Summary.** In a case of left bundle branch block, premature ventricular beats in Lead 3 and CF<sub>2</sub> in the first electrocardiogram and nodal escape beats in Leads CF<sub>2</sub> and CF<sub>4</sub> of the second electrocardiogram, taken 1 day later, revealed the presence of acute coronary insufficiency, probably infarction, which was obscured by the intraventricular block in the regular beats. There was an evolution of the inverted T waves in the ectopic beats of CF<sub>2</sub> from the first to the second electrocardiogram. Multiple ectopic beats, due to nodal escape, in the limb leads show a shortening of the QRS intervals to normal limits and a normal QRS contour. The possible mechanism is discussed. Since the mechanism producing the ectopic beats varied, it can be concluded that the pattern of myocardial infarct or coronary insufficiency may be revealed in ectopic beats in the presence of intraventricular block, to a certain degree independent of the mechanism producing the ectopic beats.

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## LARGE INTERAURICULAR SEPTAL DEFECT WITH PARTICULAR REFERENCE TO DIAGNOSIS AND LONGEVITY

### REPORT OF 2 NEW CASES

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WORKERS in the field of cardiovascular disease, particularly those interested in congenital defects, have learned during the past decade that one of the important and relatively common congenital anomalies, not previously recognized except in rare instances, is a large interauricular septal defect (I.A.S.D.). Of especial significance is the fact

that the clinical diagnosis is now possible in most cases, and yet that such a diagnosis may be a surprising discovery in a patient who has reached middle age in a fair state of health such as happened in 2 of our own cases. This fact recently excited our interest anew in the subject.

Only certain of the interauricular septal defects, referred to by anatomist and pathologist, are thought to be clinically important. Therefore, a few words are devoted herewith to the presentation of the clinical concept of this developmental defect. By I.A.S.D., as it concerns the clinician, is meant an aperture of 1 cm. or more in the interauricular septum.<sup>15</sup> Thus, only a small percentage of autopsied cases presenting an I.A.S.D. fall into this clinical classification; the larger percentage of lesser defects are of only anatomic and academic interest. Likewise, since the foramen ovale may not normally close before the 8th month of age,<sup>16</sup> such an opening found in the age group under 1 year is not regarded as clinically significant. There is much confusion in the medical literature as to the exact anatomic location of an interauricular defect. For this reason, it is often impossible to know in what part of the interauricular septum an aperture presents. Since, in the future, clinical correlation with the anatomic location of an I.A.S.D. may be demonstrated, writers on this subject had best use descriptive terminology in localizing the defect until that time when a universal and simplified embryologic classification has been devised. For example, to state that an aperture is present at the upper, middle, or lower part of the interauricular septum, meaning by "lower" that part adjacent to the ventricle, is to localize the defect clearly, no matter what the embryologic origin may be.

In 1934, Roesler<sup>19</sup> reviewed interauricular septal defects. He collected from the literature 62 autopsied cases. The youngest patient was 11 months and the oldest 75 years of age. He followed the classification of Costa.<sup>4</sup> Apparently defects measuring less than 1 cm. in diameter were not considered. Neither was this defect in combination with other congenital anomalies of the heart included in the series. The occurrence of this defect together with mitral stenosis was likewise summarized by McGinn and White<sup>14</sup> in 1933.

An analysis of the literature describing autopsied cases since Roesler's excellent review<sup>19</sup> has not been presented, although a valuable clinical paper by Bedford, Papp and Parkinson,<sup>2</sup> based on 53 personal cases (10 autopsied), has recently been published (1941). Since recognition of congenital interauricular septal defects clinically is more evident today, and inasmuch as certain new observations have been made by several authors, we have thought it worthwhile to bring the subject up to date. Thirty-one autopsied cases reported since 1933<sup>1,3,5,6,7,11,12,13,16,17,20,21</sup> (including our own Cases, 1 and 2) are clinically and pathologically analyzed. Eighteen of these cases, which ran an uncomplicated clinical course, are studied with particular reference to symptomatology and longevity. In certain instances figures from Roesler's series of 62 cases<sup>19</sup> are included for purposes of comparison. The 2 autopsied cases from this hospital are included to demonstrate an associated condition which may prove a not uncommon component

of the picture, and to emphasize the possibility of a fair length of life and considerable activity despite this defect.

**Case Reports.** CASE 1. G. S., a 43 year old native white woman had been affected since 8 years of age with gradually increasing dyspnea and cyanosis. At 35 years of age, she suffered from an attack of precordial pain which radiated down both arms; she was then hospitalized for 3 months. Similar pain, requiring hospitalization, recurred 2½ years later; there was Roentgen ray evidence of "thymus gland enlargement" for which deep Roentgen ray therapy was administered.

From the age of 39 up to the terminal illness, she attended the Out-Patient Department of the Massachusetts General Hospital at regular intervals. Her main symptoms were precordial pain (sometimes radiating down both arms and upward into the neck), usually preceded by nausea and often associated with a choking sensation, tightness in the chest, and marked cyanosis. Noteworthy physical examination findings included cyanosis, clubbing of the fingers, cardiac enlargement to the left, a precordial systolic murmur, and paralysis of the left vocal cord. The ECG showed marked right axis deviation. Roentgen ray examination revealed a "mediastinal mass" below the aortic arch and thickening of the lung hilar markings. She was completely digitalized with resultant improvement.

At 41 years of age, she was admitted to the M.G.H. as a patient on 2 occasions within a short period of time because of increased symptoms and a mild upper respiratory infection. Roentgen ray examination of the chest was described as again showing a "mediastinal mass" in the region of the main pulmonary artery. Physical examination revealed an accentuated pulmonary second sound, a blowing pulmonary systolic murmur with a corresponding thrill, and short systolic and presystolic apical murmurs.

On January 1, 1933, at 43 years of age, she was again admitted to the M.G.H. with symptoms of severe precordial pain, marked dyspnea, cyanosis, nausea, and vomiting. Physical examination findings were consistent with congestive heart failure complicated by pneumonia. Inspection revealed marked cyanosis, dyspnea, jugular vein distention, and pronounced clubbing of the fingers and toes. The blood pressure was recorded at 110 systolic and 70 diastolic. The pulse was small with a regular rate of 100 beats per minute. Respirations were labored. The left heart border extended to the anterior axillary line. There was a widely transmitted precordial systolic murmur. Moist râles were heard bilaterally over both lung fields; bronchial breathing and dullness were present over the left posterior chest. There was tenderness on palpation of the right upper abdominal quadrant. Laboratory studies were not remarkable. The complete blood count showed 11,000 W.B.C. and 6.5 million R.B.C. Urinalysis was negative. Treatment for cardiac failure was unsuccessful. The temperature remained elevated, up to 102° F. She complained of chest pain, most marked on the left, and vomited at frequent intervals. On January 15, 1933, her condition suddenly became worse and death supervened. A clinical diagnosis of (?)congenital heart disease (interauricular septal defect), (?)cor pulmonale, and bronchopneumonia was made.

**Autopsy.** Pertinent findings were confined chiefly to the heart, blood-vessels and lungs. The right ventricle was markedly hypertrophied and dilated, making up completely the anterior surface and apex of the heart. The right auricle was dilated. Enlargement of these chambers produced, respectively, enlargement to both left and right. An interauricular septal defect, measuring 3.5 cm. in diameter, was located just above the tricuspid valve. This defect was in the "exact location of the fossa ovale," and presented "in part, at least, a partial, patent foramen ovale." The left cardiac chambers were not enlarged. The valves, except for slight thickening along the free edge of the mitral valve, were normal in appearance. The pericardium was adherent to the root of the pulmonary artery. The artery itself and its branches were dilated and sclerotic. There was organized thrombosis of the left main pulmonary artery and its branches.

The lungs showed pulmonary edema and infarction in the left lower lobe. Other necropsy findings consisted of healed bilateral apical pulmonary tuberculosis, pulmonary osteo-arthritis of the fingers and toes, and slight aortic, coronary, and renal arteriosclerosis.

*Comment on Case 1.* That symptoms are not necessarily seriously disabling, and that an existent I.A.S.D. after onset of symptoms is compatible with a considerable length of life, is evident in the case of this patient who suffered from mild dyspnea for 35 years. The correct clinical diagnosis, questioned late in the course of the illness, was based upon the presence of chronic and marked right heart enlargement confirmed by Roentgen ray examination and ECG and in the absence of evidence pointing toward better explanations. The finding of a patent and unprotected foramen ovale at autopsy qualifies the statement of Bedford, Papp, and Parkinson,<sup>2</sup> that a patent foramen ovale "is clinically silent except that, when distended by increased auricular pressure ('widely patent'), it can give rise to terminal cyanosis and paradoxical embolism."

Left recurrent laryngeal nerve paralysis, present in this patient, was undoubtedly due to compression of the nerve between the dilated pulmonary artery and arch of the aorta, as recently suggested by Erlanger and Levine<sup>6</sup> in a report of 2 clinically studied cases.

A chronic cor pulmonale secondary to pulmonary endarteritis obliterans (with an incidental auricular septal defect) was thought to be a strong possibility during life, but was not confirmed postmortem; the pulmonary vascular changes were evidently secondary to the pulmonary hypertension due to the overloading of the lungs with blood and were not a primary condition.

CASE 2. J. P., a 59 year old native white woman had suffered from mild exertional dyspnea since early childhood. She married, had 3 children, and lived a full and active adult life up to the age of 45. At that time she suffered temporarily from a "nervous breakdown." She recovered from this episode and felt quite well until the age of 53 when she began to be bothered by sinus trouble and family worries. She was helped some by wintering in Florida.

In the spring of 1936, at 55 years of age, she complained of recent increased exertional dyspnea, palpitation, exhaustion, faintness on climbing stairs, and left chest discomfort. At that time physical examination revealed rather marked enlargement of the heart to the left and accentuated pulmonary second sound. There were no murmurs. The blood pressure was 115 systolic and 80 diastolic. The pulse was regular at 90 beats per minute. The ECG showed considerable right axis deviation with inverted T waves in Leads 2 and 3 and large P waves in Lead 2. Roentgen examination confirmed the percussion evidence of cardiac enlargement and, in addition, revealed prominence in the region of the pulmonary artery, an increase in hilar shadows and pulsations and left auricular enlargement. A diagnosis of an I.A.S.D. and neurocirculatory asthenia, together with climacteric symptoms, was made to explain the total picture. She gained no relief from her symptoms by digitalis, to which she was hypersensitive. However, reassurance and rest away from home were of benefit. Her course was followed closely with frequent physical examinations and laboratory check-up. A precordial systolic murmur developed within a year, her dyspnea steadily increased, and 6 months later cyanosis of the cheeks and tongue became apparent. Her circulatory condition remained stationary for several months except for the development of extrasystoles and

occasional fainting spells. In September, 1940, at 59 years of age, she felt much worse with a cold, anorexia, bouts of paroxysmal tachycardia, and a sensation of "needles in the feet." Two months later, in November, 1940, she expired after a chill and fever and a few hours of suddenly increased dyspnea and cyanosis. A clinical diagnosis was made of pneumonia complicating a congenital interauricular septal defect.

*Autopsy* (restricted to heart and lungs). The heart weighed 475 gm. The right ventricle was markedly enlarged by hypertrophy and dilatation, making up the entire anterior surface and left border of the heart. The right auricle and pulmonary arteries were dilated. An open I.A.S.D., measuring 3 cm. in diameter, was noted. The mitral valve edge was thickened and the chordæ tendineæ were markedly shortened and thickened; the other valves were normal. Examination of the lungs revealed pneumonia in the stage of red hepatization involving a portion of the right lower lobe. Microscopic examination of the lungs revealed dilated pulmonary arteries, many showing medial hypertrophy; a large number of the smaller vessels showed marked intimal proliferation. There was evidence of generalized pulmonary congestion.

*Comment on Case 2.* As in Case 1, a fair length of life with little or no serious disability was demonstrated in a 59 year old woman affected with a symptomatic I.A.S.D. for years. Dyspnea was an early and prominent symptom. Careful clinical study failed to reveal the mitral valve deformity which was found at autopsy. The correct clinical diagnosis of an I.A.S.D. was made on the basis of long-standing mild symptoms without early cyanosis, together with physical examination, and Roentgen ray and ECG findings indicative of primary right heart embarrassment.

*Date of Series Analyzed.* The frequency of an I.A.S.D., as compared with other congenital cardiovascular lesions, is high. At the Mayo Clinic,<sup>9</sup> 87 of 8134 cases (1.05%) examined postmortem showed major cardiovascular anomalies. One-quarter of these, 21 (or 0.25% of all the cases) presented an I.A.S.D. measuring 1 cm. or more in diameter; the next most common anomaly was coarctation of the aorta, totaling 16 (0.19%); next in order of frequency were cases presenting an excess of pulmonary cusps. Autopsy surveys at other institutions have likewise resulted in the conclusion that interauricular septal defects rank as among the commonest of all congenital cardiovascular defects.

The sex incidence of I.A.S.D. is not significant. In Roesler's series<sup>19</sup> females predominated, while in ours, males comprised a bare majority of 1. Nor does sex, in regard to physical activity and child-bearing<sup>19</sup> influence its clinical course.

As suggested by McGinn and White,<sup>15</sup> an I.A.S.D. of less than 1 cm. in no way manifests itself during life, and for all practical purposes should not be considered clinically significant. Rare exceptions to this rule are instances with small paradoxical emboli, which in 1 reported case<sup>8</sup> passed through a pencil-sized foramen ovale. Since 1933 only 2 cases past middle age have been reported who were without symptoms up to the time of death. One, with a defect measuring 0.8 cm., died at 77 of pancreatitis;<sup>18</sup> the other, possessing a 1.5 cm. defect, died at 59 years from complications which were secondary to paradoxical embolism.<sup>17</sup> Apparently then, most, if not all, defects which measure

over 1 cm. sooner or later express themselves clinically. The average age of death, which was 36 years in Roesler's cases and 37 years in the present series, is not influenced by size of the defect when greater than 1 cm. It is of interest, as will be emphasized later, that in cases with rheumatic valvulitis, longevity was not appreciably affected after adulthood was reached. This fact stresses the primary importance of defects, regardless of existing valvulitis, in relation to mortality. The oldest cases in Roesler's<sup>19</sup> and in our series were 75 and 68, respectively. Of the latter series 54% lived beyond 40 years of age, thus indicating a fair life expectancy despite this lesion.

The symptoms accompanying I.A.S.D. cases, as explained by Roesler,<sup>19</sup> McGinn and White,<sup>15</sup> Bedford, Papp, and Parkinson,<sup>2</sup> as well as others, arise primarily from the increased blood volume in the pulmonary circuit, which results from backward blood flow through the opening between the left and right auricles and reduces the air space in the lungs. Therefore, as might be expected, the earliest symptom in 15 of 18 carefully studied cases was exertional dyspnea. Of the remaining 3 cases, 2 were without symptoms;<sup>11,17</sup> and 1, with heart block, suffered from fainting spells prior to the onset of dyspnea.<sup>5</sup> This suggests that dyspnea as an early symptom occurs in nearly 100% of these cases. Other symptoms were not necessarily related to the heart and circulation, except as they occurred terminally due to frank right heart failure. From the onset of dyspnea in these cases the average additional span of life was 14 years, ranging from 1 to 35 years. The dyspnea was, as a rule, mild, only slightly incapacitating, and usually existed without change for years before terminal heart failure set in. As a matter of fact, this early symptom was likely to be so benign that the physician was rarely consulted until late in the course of illness. The average survival after the onset of dyspnea, in 10 cases with associated mitral stenosis, was 13 years, as compared to 14 years in 5 cases where the septal defect occurred alone. The latter fact implies that the clinical course of adults with this defect is not significantly altered by the coexistence of rheumatic heart disease.

Physical examination *per se*, except for the evidence it presents of right heart involvement, offers little or no assistance in the diagnosis of an I.A.S.D. However, together with a past history and in conjunction with other findings, it may assume importance. Since 53.8% of 93 cases included in Roesler's<sup>19</sup> and the present series showed mitral stenosis at autopsy, it is apparent that such a coexisting valve lesion should be suspected rather than rejected in every case. Cyanosis occurred in 8 of our 31 cases. It developed early in 1 instance, was a terminal finding in 3, and in the remaining 4 cases was associated with frank heart failure. Cyanosis, therefore, is usually neither an early nor a consistent finding. Murmurs were commonly heard over the precordium. They were systolic, varied in intensity and pitch, were most commonly located at the 3rd or 4th left intercostal space parasternally, and were usually not accompanied by a thrill. The murmurs were not very loud, as a rule, and could easily be considered physiologic and so of no significance. The size of the defect and the degree of

cardiac failure in most instances bore no definite relationship to the characteristics of the murmur. It is likely that a certain percentage of these murmurs was due to dilatation of the pulmonary artery, since an I.A.S.D. has never been proved *per se* to be the source of a systolic murmur. As pointed out by some authorities, a murmur produced by the defect *per se* should logically be presystolic in time; yet in only 2 of 31 patients; was this said to have been the case.

Clinical evidence for mitral valve deformity does not compare favorably with its high autopsy incidence. In our series, 19 of 31 (62%) autopsied cases showed mitral stenosis, and only 9 of these were recognized clinically. Bedford, Papp, and Parkinson<sup>2</sup> found mitral stenosis in 4 of 10 autopsies, yet they report its presence in only 4 of 43 clinically studied cases. This discrepancy ("silent mitral stenosis") may be due to the two-directional passage of blood (from the left to the right auricle as well as through a stenosed mitral orifice), which results in a reduction in blood flow through the mitral opening to a degree less than is compatible with production of an audible murmur. Therefore, just as an existing mitral stenotic murmur does not rule out an auricular septal defect, neither does its absence (along with evidence favoring a septal defect) greatly decrease the likelihood of mitral stenosis. Arrhythmias, in the form of auricular fibrillation and flutter, were reported in 7 of our 31 cases, and, in every instance, were associated with mitral stenosis.

The correct clinical diagnosis of an I.A.S.D. is being made with increasing frequency. Its clinical recognition in but 1 of 62 cases up to 1934 (Roesler),<sup>19</sup> has since increased to 14 in 31 cases (present series). The latter more desirable and encouraging figure has undoubtedly resulted from the recent, more frequent recognition by Roentgen ray and ECG examination of primary right heart involvement. Such Roentgen ray findings observed are enlargement of the right ventricle and auricle, prominence of the pulmonary arc, and increased hilar markings, especially on the right (due to dilatation of the main pulmonary artery branches). Another finding, less often present but characteristic of such a defect, is an increase in hilar pulsations, the "hilar dance."

A high percentage of these cases show right axis deviation electrocardiographically. A majority of Roesler's series<sup>19</sup> presented slight right axis deviation. It was commonly encountered in Bedford, Papp, and Parkinson's<sup>2</sup> cases. In the present series of 31 cases it was mentioned as moderate or marked in 15 instances, including our 2 M.G.H. case reports. The ECG is very helpful and confirmatory.

In the future a more certain and exact diagnosis in a far greater percentage of cases will be forthcoming when roentgenologic and electrocardiographic evidence of pure right heart disease is correlated with other clinical findings. Radiographically, the picture observed of right heart enlargement does not appear to be altered by coexistent mitral stenosis since, as already mentioned, the left auricle retains its normal size. However, an identical Roentgen ray picture of right heart embarrassment is displayed in certain extracardiac pulmonary con-



ditions such as pulmonary arteriolar disease. At this point, both the history and physical findings must be referred to in the differential diagnosis. In pulmonary artery disease, symptoms and physical examination and Roentgen ray findings parallel and approach each other in degree of severity; cyanosis occurs early and is a prominent and constant finding; after the onset of symptoms, the disease is often rapidly disabling and terminates fatally. In the congenital heart cases, on the other hand, the symptoms are strikingly mild in contrast with the rather marked evidence of cardiac involvement by physical examination, Roentgen ray study, and ECG; cyanosis, if present, is inconstant and usually makes its appearance late; dyspnea is an early and outstanding symptom and most often exists as the sole manifestation of trouble for years before the appearance of terminal frank cardiac failure. Recent reports on diodrast visualization of the heart and great vessels are encouraging from the standpoint of localization and differentiation of obscure acquired and congenital cardiovascular conditions including I.A.S.D.<sup>22</sup>

A majority of these cases die in congestive failure. Complications, resulting in death, occurred in only 5 of 18 selected cases. Only 1 patient developed subacute bacterial endocarditis;<sup>2</sup> another died as a result of paradoxical embolism following pulmonary infection;<sup>17</sup> 2 developed pneumonia<sup>2</sup> and our Case 2, and 1 patient bled to death from a ruptured varix.<sup>11</sup> There is, therefore, relative freedom from serious complications in this condition as contrasted with a majority of other congenital cardiovascular defects. Three instances of chronic pericarditis together with rheumatic endocarditis have been reported.<sup>1,3</sup> However, although the incidence of the latter is high, it has not been shown that these conditions are either directly or indirectly related to the underlying septal defect. They are, therefore, not regarded as complications, although it is quite possible *vice versa* that mitral stenosis by obstructing the blood flow may make a small interauricular defect much larger.

The pathologic physiology of an I.A.S.D. has been adequately reviewed by others as well as summarized in the preceding discussion. The heart has been adequately studied at autopsy. However, such has not been the case with respect to the pulmonary vascular system. It is of interest in this regard that pulmonary arteriosclerosis was present in both of our cases, whereas such has seldom been mentioned by others. More careful microscopic study of the lungs may aid in explaining the somewhat inconstant and variable existence of cyanosis in these cases. It is readily conceivable that early cyanosis, occasionally met with, may be the direct consequence of long-standing diffuse pulmonary arteriolar sclerosis or to complicating pulmonary thrombosis.

**Summary.** Interauricular septal defects which measure 1 cm. or more in diameter in individuals over 8 months of age are of clinical significance, and occur more frequently than do other congenital cardiovascular anomalies. Lesser defects are silent except in rare instances where they may permit the passage of small emboli from the right to the left auricle.

To avoid confusion as to the location of an I.A.S.D., the suggestion is offered that it be described as being situated in the upper, middle or lower portion of the interauricular septum.

A clinical analysis is presented of comparative studies in 62 autopsied I.A.S.D. cases up to 1934 (collected by Roesler) with 31 autopsied I.A.S.D. cases collected since that date. There appears to be no definite sex preference. The size of the lesion beyond 1 cm. does not influence its symptomatic course or the longevity. Complicating mitral stenosis, except for occasionally associated auricular flutter and fibrillation, does not alter the picture after adulthood is reached. A majority of cases is only mildly disabled from dyspnea and may withstand the ordinary physical and mental wear and tear accompanying active life for years before succumbing to frank right heart failure. The average age of death lies between 36 and 37 years, and over 50% of persons live beyond 40 years of age. Not uncommonly, individuals may pass the middle age mark without ill effects from this lesion, as demonstrated by Case 2. Complications, other than congestive heart failure, which is at times associated with terminal pneumonia, are conspicuous by their rarity. Only 1 case complicated by subacute bacterial endocarditis has been reported.

It is conceivable that secondary pulmonary arteriolar disease may develop in certain instances and be responsible for decreasing longevity. Pulmonary vascular lesions (sclerosis and thrombosis) were noted at autopsy in our 2 cases. In the future, more careful microscopic examination of the pulmonary vascular bed should be accomplished.

The clinical recognition of I.A.S.D. cases has risen markedly in the past decade. A clinical diagnosis of nearly 50% (14 of 31 cases) has been made since 1933, whereas previously only 1 in 62 cases was so diagnosed though considered in 4 other cases. Roentgen ray investigation, electrocardiography, and a recognition of primary right heart involvement has been chiefly responsible for the recent percentage increase in diagnosis.

A further step in the recognition of these cases will be possible if Roentgen ray and ECG criteria are evaluated in lieu of certain associated symptoms and signs favoring an interauricular septal defect over pulmonary arteriolar disease as a cause for right heart embarrassment. In the latter instance, cyanosis is an early constant sign, longevity subsequent to the development of symptoms is short, and physical and Roentgen ray findings parallel the clinical course. In the former, mild dyspnea, usually without cyanosis, is an early and outstanding manifestation, and there is little or no disability for several years despite physical, Roentgen ray, and sometimes ECG findings indicative of rather marked right heart involvement. With these differentiating points in mind, it is believed that the diagnosis in the future will become possible in a much higher percentage of cases.

Left auricular pressure is apparently relieved by the passage of blood through an I.A.S.D. opening to the extent that there is little or no resultant left auricular enlargement despite coëxistent mitral stenosis. The Roentgen ray picture remains that of pure right heart

involvement. Therefore, mitral stenosis should offer no barrier to the diagnosis of a coëxisting defect. On the other hand an I.A.S.D., by affecting a reduction in the left auricular pressure, frequently results in disappearance of the mitral diastolic murmur as well as of left auricular enlargement in cases with mitral stenosis, and thus conceals the latter lesion. This fact is borne out by the discovery of coëxisting mitral stenosis in 19 of 31 autopsies in contrast to its clinical recognition in only 9 of these cases.

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#### DEVELOPMENTS IN ARTHRITIS\*

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THE problem of the arthritides is entering a new phase of development. Adumbration of the ultimate nature of the problem may be in sight. This is not to state that finality of detail can now be forthcoming. It is possible, however, to perceive new relations within the problem, and to offer added justification for certain therapeutic measures whose availability and value have not hitherto had sufficient recognition.

In the minds of many practitioners recent pronouncements<sup>2,17</sup> have left therapy of the arthritides in a confused and negative phase. In order to clarify this situation and indicate the rationale of the therapeutic approach, now developing, it will be useful to consider first the

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status of certain concepts which have long dominated the field and are still influential.

Origination in this country of the doctrine of focal infection near the turn of the century resulted in early extension of it to arthritic diseases with many beneficial results. Recognition of this relationship led to application of the apparent therapeutic corollary to it; namely, the use of vaccines. Contemporaneously, attention then extended to the use of non-specific protein and a host of cognate injections and measures, depending upon superficial or systemic reactions of greater or less severity. Throughout all of this period, which has lasted about 40 years, the dominant concept underlying the problem, at least of atrophic or rheumatoid arthritis, was infection, focal or otherwise. The chief approach to study of the disease was bacteriologic, and out of the experiences thus acquired grew some significant observations, such as those concerning sensitivity and agglutination and precipitin reactions in rheumatic disease.<sup>3</sup>

Establishment of atrophic arthritis as primarily a bacterial disease has not been possible, however, in spite of intensive and extensive efforts to this end.

With the passage of years, failures inherent in overemphasis upon focal infection and vaccines engendered skepticism and finally disapproval of them as significant factors in the treatment of arthritics. Indeed, in some quarters focal infection is now completely in the discard, even as a contributory factor to the arthritic syndrome, and there is grave danger that opinion will swing so far in this iconoclastic direction as to deny to arthritics advantages resulting from dispassionate evaluation of it. There will be the less excuse for such overaction, in that, shortly after the last war the writer and his associates<sup>10,11</sup> pointed out that infection, although important, could not be regarded as the basic cause of the problem and that many deviations of physiology deserved equal and, indeed, greater attention.

Thus, the clinician, the general practitioner in particular, is left at present with virtual elimination of the premises upon which he thought the problem rested and has little more than heat, massage, anodynes and, the "dernier cri" of the day, gold, with which to approach treatment of arthritics. It is therefore a purpose of the present article to show where new premises can be sought and to integrate new as well as some old factors into a brief but rational outline of therapy.

In 1928 the American Committee for the Control of Rheumatism expressed its belief that arthritis is a generalized disease with joint manifestations and is not primarily a disease of joints. This pronouncement has had general acceptance, but there has been relatively little inquiry as to the nature of the "generalized" process or processes concerned. Over a period of many years, however, there has grown up a considerable body of clinical evidence to suggest that disturbances in the great systems of the body, meaning chiefly the nervous, vascular, hemopoietic, and gastro-intestinal systems, are caught up in the disease, or basically underlie it, or both. Of these the deviations or

dislocations occurring in the nervous system are among the most graphic. In this connection it is common knowledge that some of the manifestations of the nervous system are mediated through the endocrine chain.

Some cases of arthritis are recognizably related to certain endocrine functions, especially gonadal. "Climacteric arthritis"<sup>11</sup> and "arthritis of the menopause" which have been encountered in the literature since 1855 are familiar designations. The temporarily beneficial influence of pregnancy upon the arthritic woman has also become more widely appreciated and the exacerbating effect of menstruation is known even to the laity. These several influences have usually been regarded, however, as contributory or aggravating rather than as reflecting a background of etiologic significance. This limited point of view is clearly indicated by the fact that, although the above relationships have been recognized for 50 years or more, research and therapeutic experimentation in arthritis have been during that period predominantly within the bacteriologic field.

The increasing availability and use of estrogenic substances within the past 6 to 8 years have served to strengthen the suspicion that certain varieties of arthritis derive from some imbalance of the gonadal hormones. This view has apparently been easy of acceptance for hypertrophic or osteo-arthritis which has been widely designated as a "degenerative" disease, but less easy for atrophic or rheumatoid arthritis which has been equally widely regarded as basically referable to infection.

Impressed by the potential importance of the relationships just mentioned, within the neuro-endocrine systems, to both great types of arthritis, atrophic and hypertrophic, the writer, in conjunction with C. W. Scull, endeavored recently to integrate known and hypothetical considerations, germane to the above field, in the form of a chart or diagram, having for its aim a better visualization of the arthritic problem as a whole.<sup>12</sup> It is recognized that such an ambitious attempt must fall short of its goal and reflect inaccuracies. It is also recognized, however, that most of the premises on which it is based reflect accepted physiologic dictum.

Development of the concept of psychosomatic medicine in the mind of the profession at large will perhaps prepare some readers to entertain more sympathetically than they otherwise might the considerations here advanced.

There is significant evidence for the view that the 2 great groups of the arthritides, atrophic and hypertrophic, together with certain other aspects of rheumatism, are at least partly referable to imbalance within the neuro-endocrine chain. There is no opportunity here to review this evidence in full; but, to illustrate the general principle under discussion, the following paragraph from the chart and publication referred to may be quoted. "Stimuli or factors such as heredity, physical activity, nutritive defects, infection, trauma and exposure may be conceived as impinging on a central mechanism. The factors comprising this mechanism are the great systems of the body, inter-

TABLE 1.—POSSIBLE RÔLE OF PRECIPITATING FACTORS ACTING SINGLY OR IN COMBINATION, IN PRODUCING SYMPTOMS OF CHRONIC RHEUMATIC DISORDERS THROUGH THE MEDIATION OF "CENTRAL FACTORS"

Precipitating or sustaining factors	Components and functions of neuro-endocrine system affected	Symptom-complex resulting in the arthritic	Type of arthritis involved
Infection, toxemia, hereditary imbalance, physiologic "draft," "starvation," vitamin deficiency	<i>Hypofunction of the adreno-tropic factor of the pituitary</i> or Adrenal cortex	Increased susceptibility to infection, toxins, histamine  Asthenia Fatigue Hypotension Low BMR Caries	A and H  A A and H A A and H A and H
	<i>Hypofunction of the growth factor of the pituitary</i> or	Asthenic build Decreased capacity for protein synthesis Secondary anemia Demineralization	A A and H  A
	<i>Hyperfunction of the growth factor of the pituitary</i>	Calcification of cartilage Osteophytes Phalangeal enlargement Paresthesia Megalocolon Sthenic build	H H H  H H
Menopause	<i>Hypofunction of the thyro-tropic factor of the pituitary</i> or Thyroid	Low BMR "Dry" skin	A and H H
	<i>Hyperfunction of the thyro-tropic factor of the pituitary</i> or Thyroid	High BMR	
	<i>Hypofunction of the gonado-tropic factor of the pituitary</i> or Gonads	Emotional instability Sweating "Flashes" Fatigue Vasomotor instability Arthralgia Headache Hypertension	A and H
Pregnancy	<i>Hyperfunction of the gonado-tropic factor of the pituitary</i> or Gonads	Relief of symptoms	A
	<i>Hypovasopressor function of the posterior pituitary</i> <i>Hypervasopressor function of the posterior pituitary</i>	Low blood pressure, decreased peristalsis Decreased skin capillary flow Edema Water retention	A and H
Mechanical pressure by capsular distention, tissue swellings and bony overgrowth	<i>Nervous system</i> Pain fibers	Pain	A and H
Nervous stress or strain from: worry, excessive activity, trauma, exposure to cold	<i>Vegetative nervous system</i> Increased adrenergic response through epinephrine	Peripheral vasoconstrictions Hyperglycemia Relaxation of gastro-intestinal tract	A and H
	Overactivity of sympathetic system	Reduced resistance to fatigue—cold Decreased BMR Poor regulation of body temperature	A
	Increased cholinergic response through acetylcholine	Increased gastro-intestinal tone Flushing Palpitation Sweating—general	
	Overactivity of para-sympathetic system		

related, as they are known to be, through the central nervous and endocrine chains. Many of the objective phenomena of the rheumatoid syndrome can be seen to consist of phenomena which reflect, to some extent, normal activities of the systems concerned. It is, therefore, tempting to endeavor to relate some of these phenomena, as exhibited in disease, to under- or overaction of the systems or organs having comparable or parallel functions. No attempt to this end could be regarded with finality, but it is rather surprising to observe the extent to which such an hypothesis affords a working explanation of many otherwise apparently unrelated symptoms. The symptom-complex constituting rheumatic disease, regarded in this manner, may perhaps be better described as a Mesodermosis, since practically all of the tissues primarily involved are derived from the Mesoderm."

Since publication of this chart, there has appeared a report by Selye *et al.*<sup>20</sup> on the production of certain arthritic phenomena by injections of desoxycorticosterone into adrenalectomized and thyroidectomized, as well as normal rats. It is also to be noted that for some years Silberberg<sup>21</sup> has reported the induction of phenomena suggestive of hypertrophic arthritis following the administration of anterior pituitary to experimental animals. These several observations constitute a new experimental approach to the syndromes of arthritis and rheumatism, and help to lift these topics out of the restricted angle of contemplation in which they have long resided.

However suggestive the observations just recorded, the complexity of such experimentation will require time for exploration, not to say therapeutic fruition; if, indeed, this is to supervene. In the meantime, it is desirable that an attempt be made to correlate the various aspects of the problem under discussion with actual clinical experiences illustrative of them, with the aim of advancing therapy of living arthritics.

Effective therapy of arthritics requires a regimen of "total support" of the patient.<sup>13</sup> There are obviously 2 therapeutic aspects to total support; one, in general, removes from the field such accessible factors as make for or constitute worry, fatigue, faulty body mechanics, faulty nutrition and focal infection; the other seeks to provide constructive factors such as rest, correction of anemia, replacement therapy in the gastro-intestinal or endocrine system; tonic medication, sedation, physical therapy, and optimal nutrition. Obviously these objectives and measures overlap.

Recognition of the operation of neuro-endocrinous influences in the syndrome as a whole, and in a regimen of total support in particular, not only contributes to a rational concept of the nature of the disease but also serves to bring into better perspective a number of valuable therapeutic practices.

In illustration, the following cases, out of many, are cited, but they could hardly be regarded as more than sporadic examples unless scrutinized against the background of the probable explanation of them. In this light they reflect certain etiologic and therapeutic principles not often to be observed so free from complications to cloud the

issue. Grollman<sup>5</sup> remarks, "It is only the most striking changes (in neuro-endocrine relations) which draw our attention, while milder and more subtle effects escape notice."

**Atrophic Arthritis.** CASE 1. Dr. R. F., physician, aged 32, married, with 2 children, came to the office on December 23, 1941. He weighed 250 pounds, and was of the stocky, muscular type. He had played on a leading Eastern college football team and had since conducted a general practice, including maternity work. He was also engaged in defense war work.

His chief complaint was pain in the right knee, but the total distribution included the right shoulder, right ankle, and left wrist, together with generalized pain and stiffness in the morning. For the past 3 or 4 years he had had transient arthritis and migraine, especially after colds. The first serious attack of rheumatic nature followed a strep throat a month ago. There was a history of intestinal stasis. His father had had some rheumatism in the legs and his mother had been subject to migraine. The patient was himself subject to the allergic influence of a lucite wrist-watch band. The tonsils were out and he denied genito-urinary infection.

The physical examination was essentially negative except for the tongue, which was slightly coated. The patient could bend well but the lumbar spine was somewhat stiff. The gall bladder was negative to dye study and the basal metabolism was normal. There were reduplication and redundancy of the pelvic portion of the colon, a contour of spasticity and irritability, and moderate dilatation of the right half. The blood count was normal; the sedimentation was 20 mm. in one hour; the albumin-globulin ratio was 1.6; the cholesterol was 234; serum uric acid 4.5. Examination of the mouth showed a gingivitis of Class 2 (in a scale of 4); the nose and throat and genito-urinary tract were negative.

During the period of about 2 weeks within which the patient underwent the necessary examinations, he felt generalized pains in the feet, shoulders, knees, wrists, and elbows, which were worse. The patient said he felt "happiest" when under the influence of salicylates and had been taking 90 to 100 gr. of sodium salicylate a day, the usual prescription being sodium salicylate gr. 15, sodium iodide gr. 1; every 3 hours and once at night.

The indications in this case were clearly to reduce the activities of the patient, prescribe standardized periods of rest, light sedation, modify the diet as regards excess of carbohydrate since he was a large eater, cut down the salicylates, and attend to the gums.

The patient returned to his work carrying out instructions, and was next seen on June 16, 1942. He then said that he had felt very well after a month of treatment. About June 1 he had played golf and developed a lame back which cleared up after 1 week. The patient was spending 9 hours in bed at night and was taking a rest of 1 or 2 hours in the afternoon but no medication of any kind. At this period he said that he felt less "confident" than before the arthritis developed and had less "punch" but was not so fatigued. He was advised to cut down on coffee and to omit smoking. The patient said that he had been definitely surprised by the beneficial effect of rest and less work.

The patient was next heard from on May 23, 1943, at which time he wrote the following letter: "My arthritis has cleared up completely. Surprisingly enough to me, rest, as you suggested, seemed to be the answer. . . ."

On November 7, 1943, he wrote as follows: "I recently applied for a Commission as Lieutenant in the Army. . . . I have had no arthritis since I last communicated with you."

CASE 2. Dr. P. C., physician, aged 40, came to the office on November 11, 1941, complaining of pain in the right shoulder and general fatigue. The pain had begun suddenly 15 months previously, though 5 years before that the right wrist had been involved in the same way, and 10 to 11 years ago he had had rheumatic pain in the sternum. The condition as a whole had been worse in the last 5 months. The total distribution of disability was both



shoulders, both hips, both knees, lumbar-thoracic junction of the spine, and the left hand. The patient thought that the precipitating factors were fatigue and infection of a lingual tonsil in April, 1941. He regarded himself as a nervous individual and suffered from considerable insomnia because of pain in the shoulder and nocturia due to nervousness. He had been costive for 20 years.

He had had some dead teeth, had nerve deafness in the right ear; an appendectomy in 1910; and removal of tonsils and adenoids in 1920. In 1920 he had had an operation on the inferior right maxillary sinus; the left had been washed out 21 times. He complained somewhat of vertigo upon sudden change of position and also of tinnitus in the left ear. Nine years previously he had had Ménière's disease which lasted for a total of 5 years. He had also had a bilateral sphenoidectomy and removal of tonsil stumps in 1934.

Roentgen ray of the right shoulder showed a small calcified area in the supraspinatus tendon. The patient had attended a leading spa the previous summer but had been made worse. He had had intravenous injections of salicylates and iodine and had also had colchicine and short-wave diathermy. He had also been given Ertron, 50,000 units t.i.d. 6 months previously without benefit. Three months before being seen he had taken thiamin chloride, 10 mg. t.i.d., with increased appetite, but no effect upon the pain. He had not smoked for 10 years except occasionally. He was moderate in the use of alcohol. The physical examination was essentially negative and full blood studies showed no abnormalities except that the sedimentation rate was 60 mm. in 1 hour.

The nose and throat examination (November 21, 1941) revealed a pansinusitis which had cleared up but now showed reinfection and an acute ethmoidal involvement with empyema. The dental examination revealed a gingivitis of Class 2 and 3 (in a scale of 4). Genito-urinary examination was normal upon 2 occasions as was also the gall bladder under dye study, but the colon showed a contour of spasticity and irritability.

The patient volunteered the statement that eating much candy gave him arthritic pain the next day, but said that nevertheless he was a large eater of sweets.

He was cautioned about overwork, told to reduce his activities, to retire early, and to rest, regularly, 1 hour o.d. flat on his back. He was given phenobarbital,  $\frac{1}{4}$  gr. q.d., tincture of nux vomica, mms. 3 t.i.d., and he was advised to hold down somewhat the dietary purines since the uric acid was 5 mg. per 100 cc.

The patient was seen in 2 weeks and volunteered that the sedation, rest and change of diet, especially the first two, had helped greatly.

On December 23, 1941 he reported that he had had baking and massage to the shoulder which was improved. No treatment had been given to the gums, sinuses or teeth. He said that he no longer ate candy and thought that quiet, rest and phenobarbital had helped most, stating, "I am getting better on next to nothing."

On January 20, 1942, he said that he had been doing well until the past week when he had had an attack of grippe and had felt pain in the hips and lumbosacral region. He had missed the daily rest of 1 hour for the previous week—"I was too busy, seeing 43 patients in one day." He was up at 9 A.M. and went to bed at 10.30 P.M., exhausted. Nothing had been done as yet about the teeth or other foci, and there had been no baking or massage to the shoulder recently but more motion and function were present. He had less sinusitis, was less costive and was less nervous. The blood pressure was 160/100.

On November 30, 1943 he had some stiffness in the hands, and realized that he should persevere in the original recommendations laid down, but was nevertheless carrying on a busy practice and regarded the advice again given him as having theoretical rather than necessitous significance. An ECG taken 1 month previously was normal. The patient was taking little or no medicine except, occasionally, phenobarbital, gr.  $\frac{1}{4}$ , extract belladonna, gr.  $\frac{1}{4}$ .

This case offers a clear-cut example of atrophic arthritis in its relatively early stages, in a busy practitioner, complicated by foci of infection, some

increase in blood pressure, an irritable nervous system and a condition of the gastro-intestinal tract verging on spastic colitis.

In spite of the above complications or contributory factors, some of which would have been universally regarded as the essential etiologic factors only a few years ago, this patient experienced a dramatic improvement on the basis of "physiologic" adjustments and was even able to carry on his practice without serious interruption. Good practice really required that the patient renounce most or all of his work, enter upon a programme of complete rest, care for the infection present, and generally conform to the recommendations set forth in Table 3. The case is chosen, however, to illustrate how influential the simplest of measures may be even though carried out with less than the recommended thoroughness. This experience is not to be regarded as justification for such laxity.

CASE 3. MRS. L. E., aged 55, presented herself on January 31, 1939, with almost complete fibrous ankylosis of the fingers of the left hand due to atrophic arthritis. About the only useful motion left was a slight amount between the thumb and forefinger, and the hand resembled a fin. There were discomfort and angulation at the left elbow. The left shoulder, the knees and left sacro-iliac joint were also painful. She complained of paresthesias of the toes and of muscular twitching which frequently awakened her at night.

There were edema of the left hand and tenderness over the manubrium at the junction of the costal cartilage. The external malleoli were puffy; the left hip rotated with tenderness; there was some descent of the lumbar spine upon complete flexion of the left femur and there was tenderness at Poupart's ligament on the left and at the left iliac crest. There was also tenderness at the 7th cervical and 5th thoracic vertebrae. The throat was dry and glairy with a history of catarrh, and the nurse stated that the patient was very nervous and smoked from 1½ to 2 packs of cigarettes daily.

At the age of 11, the patient's knees would swell in winter as they did again at 14 after diphtheria antitoxin; during the past 3 winters she had also had stiff knees most of the time. Both sides of her family had had arthritis, and on her father's side there was psoriasis, which the patient also presented. There had been intestinal stasis for 22 years and many attacks of tonsillitis. Two infected teeth had been removed 4 or 5 years ago. The patient was physically fatigued. She was a large eater of rich foods and disliked greens and fruits. At one time she had been in bed for 3 weeks for a condition diagnosed as "colitis" and had had many "cures" abroad.

A year previous to admission she had had 2 attacks of vertigo. She had had a tonsillectomy some years before as well as an appendectomy and a repair operation. The removal of 2 teeth had helped the right arm and shoulder, although later she had had 8 injections of streptococcal vaccine. She had also had short-wave diathermy, general massage and colonic irrigations. At one recent period she took 5 grains of aspirin and ½ grain of codeine sulfate every 4 hours for 4 months. Of late the patient had been taking 30 grains of aspirin every 24 hours.

The significant laboratory findings were as follows: Basal metabolism minus 23; sedimentation rate 23 mm. in 1 hour, on a scale of which 12 mm. in 1 hour was the normal limit; cholesterol 270. There was a Class 2 gingivitis (in a scale of 4). The nose and throat showed evidences of previous inflammation in the sinuses, but were free from infection at the time of examination. The Roentgen ray showed a spastic colon, marked demineralization of the left hand, and a classic picture of atrophic or rheumatoid arthritis.

This patient, who had been ambulatory, was put to bed and kept there. She was given mild sedation together with gentle stimulation with tincture of nux vomica. She was given a diet high in protein, reasonably high in fats and somewhat restricted in concentrated carbohydrate foodstuffs. This diet was also high in vegetables and fruits which were usually put through a colander to avoid undue roughage. She was also given accessory vitamins and was required to stop all smoking. Heat and gentle effleurage were administered to the involved parts.

From the start she began to evince improvement as indicated by less tenderness, freer movement of the fingers, fuller extension and motion of the left elbow and also diminished pain and freer movement in the left shoulder.

After 3 weeks she was given Armour's thyroid extract, gr. 1/5 twice a day. It is to be noted, however, that she had made a definite advance before getting this and also that 20 years before, after a B.M.R. test, the patient had taken thyroid for some months.

The result in this case was that this patient made a complete recovery except for the destruction of cartilage and the fibrous ankylosis already present. She kept under sporadic observation and remained well for 2 years.

On September 28, 1943, this patient presented herself again, with a history of having fallen and suffered a Colles' fracture of the right arm. The fracture had been treated by an orthopedist who put the arm in a plaster cast. After 4 weeks the cast was removed and it was found that all of the fingers of the right hand had reached a condition closely resembling that presenting in the left hand, except for added tumefaction, edema, etc., on the fractured side. It was clear that the processes of atrophic arthritis in the hand were intense and were leading to complete incapacity of it. No prehensile motion was left except slight approximation of the forefinger and thumb. Several of the mid-joints of the fingers showed distinct tenderness upon lateral pressure.

Upon observing the condition of the right hand when the cast was removed, she consulted a well-known rheumatologist who advised her to undergo a course of gold salts. Having acquired some knowledge of arthritis through her previous experience, the patient believed that such a step would be unwise and did not enter upon it.

She had been leading an active life prior to the accident but was at once placed under conditions of restricted activity and enforced rest. The basal metabolism was still minus 25, the cholesterol was now 427 mg. per 100 ml., and the sedimentation rate was 53 mm. in 1 hour. The blood was otherwise negative. Physical therapy was begun in the form of baking and massage to the fractured hand and arm. She was again given mild sedation, gentle tonic stimulation and accessory vitamins. She was placed upon a diet balanced as before and from the start began to make significant progress. Consultation with Dr. Charles W. Dunn in respect to endocrine imbalance resulted in the conclusion that this patient was suffering from a long-standing anterior pituitary deficiency, and she was given: Anterior pituitary, gr. 1; Thyroxin 0.15 mg.; Calcium glycerophosphate, gr. 5 b.d. It was recognized that there is division of opinion as to the efficacy of anterior pituitary administered per oreum.

By the latter part of April, 1944, the right hand had almost achieved the condition of the left, having lost nearly all of the excess tissue fluid. There had also been achieved some approximation of the first fingers and thumb on that side so that both hands now functioned in limited but almost identical manner. At this point the patient volunteered that notwithstanding her inability to use her hands normally, she felt happier and more serene than ever before in her life.

This case conveys important lessons. In the first place, upon the first admission the patient started to make a significant return to health without the intermediation of replacement therapy in spite of the fact that for years she had had a low metabolism and had once been given replacement therapy for it.

In the second place, after full clinical recovery from this episode, it is clear that some background for recrudescence of the arthritis was still present. The fracture, followed by the application of a cast, together with the fact that she had not been living her life as "physiologically" as she should, permitted the arthritic process again to become active. It is obvious that the treatment instituted for this fracture by means of a non-removable cast was faulty and open to major criticism. If the hand had been put in a removable cast and had been given baking, effleurage and, later, massage during the

period of incarceration, the fibrous ankylosis characteristic of atrophic arthritis would probably not have developed.

The addition of endocrine therapy contributed to the rapidity of later convalescence but was not the sole or determining factor in this. In fact, on April 26, 1944, the basal metabolism was still minus 25. It is of much interest to note that, in spite of a dosage of thyroxin beginning March 22, 1944, of 0.30 mg., and increasing on May 11, 1944, to 0.35 mg., a hormonal assay on May 30, 1944 (conducted in collaboration with Dr. A. E. Rakoff), showed the following multiple imbalance, representative of a severe postmenopausal state: Urinary gonadotropins in international units per 24 hours—more than 100 (markedly excessive); urinary estrogens in mouse units per 24 hours, 6 (diminished); urinary 17 ketosteroids—1.8 mg., equivalent androsterone per 24 hours (diminished). The high gonadotropic assay is not out of keeping with the clinical opinion of anterior pituitary deficiency, since it reflects only one of several activities. The relationships here concerned will be made the subject of a later contribution.

In sum, this case is, therefore, an outstanding example of the fact that atrophic arthritis may be accompanied, and was apparently induced in this instance, by imbalance of a clear-cut endocrine nature. To meet this deficiency the patient had in the past been given thyroid. When first seen, the thyroid had long been stopped and marked convalescence was then initiated even in the absence of thyroid medication. Full recovery ensued. The full cycle of arthritis of the hand, following fracture, was then repeated, again followed by recovery.

This experience illustrates the efficacy of the therapeutic principle of achieving better equilibrium in the major systems of the body and also presumably in the endocrine chain. Partial replacement therapy was later useful but was never pushed to the point of complete replacement.

**Hypertrophic Arthritis.** CASE 4. Mrs. Wm. M. S., aged 63, was admitted to the Hospital April 2, 1941. Her chief complaint was in the fingers, which showed the beginning formation of Heberden's nodes. The present illness dated from August 8, 1940 when she had had sulfanilamide for a severe tonsillar infection. This was followed by generalized rheumatic pains for which she was in bed for 6 weeks. She had also had a course of streptococcal vaccines and diathermy and had had more pain in the past 2 months. One brother had had rheumatic fever and 1 daughter was said to have had rheumatic fever at the age of 7. The patient had been very active in sociologic work. She was a rather large eater.

The physical examination was essentially negative except that the right kidney was palpable in the first degree, and the blood pressure was somewhat elevated. The blood, sedimentation rate and basal metabolism were normal. There was a Class 2 gingivitis (in a scale of 4). The cecum occupied a transverse position and the descending colon lacked haustration.

The patient was kept in bed and given gentle sedation while her case was being studied. From the start she made a marked advance and then experienced decreasing tenderness in the hands. She was then placed upon a well balanced ration to be described later, and local treatments were carried out upon the tonsils and gums. After 12 days in the hospital she returned to her home with strict injunctions to adhere to the regimen instituted at the hospital.

She was readmitted to the hospital for a "checkup" on June 24, 1942, at which time she had been free from arthritic symptoms since the previous admission. She had been too active in war work, however, and the blood pressure was too high, being 180/90. This patient was seen several times in the course of the subsequent year, at the end of which time she was still in excellent health. This case illustrates the fact that there may be no clear-cut evidence of endocrine deficiency as manifested by the basal metabolism,

although the cholesterol at the time of the first admission was as high as 331. The relatively minor changes in this patient's way of living, imposing also some restraint upon her physical activities, relieved her of all symptoms.

CASE 5. Mrs. M. T., aged 65, entered the Hospital April 28, 1943, with definite evidences of hypertrophic arthritis, complaining chiefly of pain in the hips and thighs, especially the right. The hands showed Heberden's nodes. The duration of symptoms was about 14 years. The previous summer had been strenuous for the patient due to the illness of her husband, and the pain in the right thigh and hip had been so severe that in the spring of 1943 she had to spend 2 weeks in bed. The heart showed evidence of slight myocardial damage; there was tenderness of the vastus externus on the right. The right thigh flexed freely but on external rotation there was pain in the vastus externus. The same was true of the left thigh, though less so. There was pain in the left heel and she could bend only two-thirds of the normal range. She presented a slight degree of spasmus nutans of the head.

Roentgen rays showed narrowing of the joint fissure in both hips with moderately advanced hypertrophic changes in the sacro-iliac joints. There was well advanced hypertrophic arthritis involving the intertarsal joints, with a spur 3 to 4 cm. long on the left heel. There was an osteophyte on the articular surface of the right tibia with spur formation on the left.

There were a Class 2 gingivitis (in a scale of 4) and chronic tonsillitis with pus in the right tonsil. The blood was negative and the sedimentation and B.M.R. were normal.

Upon admission she was at once placed upon a regimen of complete confinement to bed, gentle sedation, and a well balanced but not "excessive" diet. Twelve days after admission she was much better; the legs had lost nearly all tenderness and the hands looked collapsed. Three days later an infected tooth was removed.

The immediately precipitating factors seemed to have been overactivity and nervous strain, complicated possibly by infection in the tonsils and mouth.

The patient returned home about a month after admission, greatly improved, with strict injunctions to follow rigidly the regimen instituted at the hospital. This she did, with the exception of periods when the illness of her husband required that she sacrifice herself in his behalf, and remained essentially free from discomfort, and able to carry on with efficiency, when last heard from in May, 1944.

This patient had been seen in 1931 and 1932 with comparable complaints, from which she made such a gratifying recovery that she was lost to observation for over 10 years. The treatment followed on those occasions was identical in principle with that described above. The evidence of hypertrophic arthritis in the hands had increased in the years which had elapsed but the patient volunteered that she had grown careless with her regimen. The last admission in 1943 is first cited because the picture of hypertrophic arthritis is more adequately illustrated.

This case reflects a clear-cut example of hypertrophic arthritis in which no specific evidence of endocrine deficiency was available and hence there was no clear indication for specific replacement therapy. There can be small doubt that the patient belonged in that group of cases referable to imbalance in the neuro-endocrine system, but achievement of the "equilibrium" discussed sufficed to inaugurate and maintain convalescence.

Some reflections of Cases 1 and 2 presented here are being encountered in the Armed Forces, at least in this country, and a similar situation was experienced in the last war. These cases present difficulties of diagnosis as to type and especially of disposition. They may present few Roentgen ray evidences and they stop short of the typical picture

of either atrophic arthritis or rheumatic fever. In the last war these cases were included in an extensive survey of arthritics in the army,<sup>10</sup> and it was found that many of them originated through "exposure" which constituted the etiologic factor in 60% of the whole series. It was also noted that five times more men recovered in the presence of focal infection than recovered after the removal of it. This experience brought sharply to mind the fact that elements other than infection must be at least contributory to the syndrome, although at that time it was regarded as heresy to question the etiologic rôle of infection. In 1941, Halliday<sup>7</sup> called attention to somewhat comparable cases which he termed psychosomatic rheumatism, and more recently Boland and Corr<sup>1</sup> have discussed the occurrence of certain types of rheumatic disability in the Army under the title of Psychogenic Rheumatism. The writer has seen many similar cases in the army hospitals of the present war and has been repeatedly questioned by medical officers as to proper classification of them. These cases obviously constitute in the Armed Forces a sort of laboratory experiment in the induction of arthritis. The factors bringing it on, at least in this country, are largely those also present, in principle, in civil life. However, in peacetime, few large bodies of young men are long subjected to comparable intensive strain, both physical and mental; a fact which doubtless accounts for the small numbers of these cases encountered in civilian clinics.

The striking figures from the last war revealing the high percentage recovery of the large group studied in the course of a few months after they had been invalidated, is probably referable to recuperative processes operative along the general lines discussed in the present text. There has not, as yet, been enough experience in these cases to justify strong postulates regarding them, but it is probable, on the basis of such instances as form, in part, the substance of this article, that at least some cases developing in the Army need in principle the kind of therapy outlined above.

It is also possible that psychiatric examination of these individuals would throw light upon the situation as a whole.

In reviewing the above group of cases from civil life no great single deviation stands out in the congerie of influences operative, and the situation is rather one in which apparently minor deviations disturb normal physiologic relationships. Analogy to this can be seen in the field of nutrition, where partial avitaminoses may be induced by extraneous factors which exert an influence upon the conditions of the nutritional equilibrium rather than upon the amounts of vitamins *per se*. Experimental animals fed rations which are antiscorbutic, under resting conditions, will develop scurvy on the same diet if exercised. This is equally true of other vitamins and of other precipitating factors, such as infection, or a diet excessive in one of its constituents.

Some explanation is now available as to the *modus operandi* of certain steps which should be basic in the therapy of arthritis. Thus, there is subscription, among a few close students of the subject, to the view

that rest is prerequisite to successful treatment of the sick arthritic, but it is to be doubted whether this viewpoint often extends beyond injunctions to "take things easy," or that it actually requires that the patient stay in bed under a strictly balanced regimen. It is, furthermore, definitely clear that such practice has not extended widely among the profession as a whole, to the great cost of arthritics, especially in the early and formative stages of the disease.

A recent survey of the kinds of therapy practiced by physicians treating arthritics revealed that less than 11% prescribed rest. Many patients of the writer's series had been previously advised to keep moving their joints "even if it hurts, so that they will not get stiff." The issue involved here may be very confusing to both physician and patient. The greater mobility induced by movement and exercise is only temporary, due to the "hyper-physiology" and increased blood flow brought about, and results in added trauma and damage to the part. The postural exercises recommended to be taken even in bed (Tables 2 and 3) are carried out within sharp physiologic limitations and constitute a different issue.

TABLE 2.—CONDITIONED REST

1. Conditioned rest is not mere negation of activity; as such it could be harmful in many ways.
2. In rheumatoid or atrophic arthritis it may lead to ankylosis unless controlled.
3. Most patients undergoing rest should experience some form of physical therapy, postural exercise, or be allowed up for brief periods daily.
4. Properly conditioned rest, in bed—
  - (a) promotes passage of tissue fluids into the vascular channels;
  - (b) promotes opening of peripheral capillaries because of warmth induced by the bed clothes;
  - (c) promotes relief from static strains incident to maintenance of the erect posture;
  - (d) promotes relaxation of the nervous system;
  - (e) allows ptosed organs to assume proper position and function;
  - (f) reduces metabolic load;
  - (g) permits settlement of metabolic deficiencies.

TABLE 3.—GENERAL ORDER OF TREATMENT

1. Rest, systemic as well as local
2. Psychic evaluation
3. Sedation and/or stimulation; *never opiates*
4. Optimal nutrition in a refined sense, including accessory-vitamins if necessary
5. Proper gastro-intestinal function
6. Examination of the blood and body chemistry
7. Time for establishment of a general equilibrium
8. Psychic reëducation
9. Examination for foci of infection
10. Medication, such as iron, arsenic, nux vomica
11. Replacement therapy when indicated
12. Treatment of foci, conservatively
13. Use of physical therapy, conservatively—chiefly heat, gentle massage, postural exercise
14. Orthopedic help
15. Last, if at all, gold, vaccines, non-specific proteins.

Analysis of the influence of rest reveals that rest is more than mere negation of activity and is composed of constituent parts, each of which is a topic for scrutiny in itself. Some of these topics afford a "raison d'être" for the present contribution. In Table 2, setting

forth the components of rest just discussed, it will be observed that the several components specified reflect, in part, changes taking place in the vascular and nervous systems. Some of these changes can be observed clinically by anyone, and were made a goal in that therapeutic approach to treatment of the arthritic by the author and his associates which attempts to bring about a better equilibrium in the major systems of the body.<sup>14</sup> This goal still remains the clinical desideratum, and "en faute de mieux" in the way of specific accomplishment, is still to be sought. Particularly graphic, because early visible, is the diminution of the tissue edema, especially of the hands, which may ensue within a few days.<sup>8,18,22</sup>

The necessity for a period of recuperation can be observed in many conditions involving imbalance of the neuro-endocrine chain. Thus, exhaustion of the adrenals of experimental animals through exposure to heat or cold causes a demonstrable disappearance of osmic acid-reducing substances.<sup>4,19</sup> Infectious, toxic, or metabolic diseases cause a loss of lipoids and vacuolization of the cells. The characteristic doubly refractive substance of the cortex vanishes under conditions of exhaustion and increases under conditions of rest. Many other illustrations could be adduced.

To date, therapy in the endocrine field has been chiefly concerned with "replacement" therapy and less concerned with reestablishment of normal relationships between the several links of the chain by means of decreasing the "load" so that dysfunctioning factors may operate within the limits of their normal potential. Full use is made of this principle in cardiovascular disease, for example, but scant use is made of it in arthritis. When practiced, however, a very few days may suffice, in some cases, to change the overall picture of acute, active arthritis to one of abatement. Clinical corroboration of the general viewpoint here discussed is to be seen in the adjuvant use of gentle sedation, free from any anodyne influence, and in the use of mild "tonic" stimulation. These apparently opposing influences are not incompatible. As regards sedation, it is difficult to say what phases of the cerebrospinal axis and endocrine chain are most usefully or "specifically" affected. In some cases, when first seen, the psyche may be unduly excited, but in others there may be the most reasoning calm. In nearly all, however, gentle sedation under conditions of bed rest may have surprising consequences. This statement is not to be interpreted as constituting a formal or isolated therapy of arthritis, but as an illustration of the extent to which basic factors within the neuro-endocrine system are open to favorable influence even though "replacement" therapy is not indicated or available.

The better equilibrium of and between the major systems of the body which the writer and his associates have frequently stressed, now appears as the "external" consequence, in part at least, of a better equilibrium of and between the component structures of the neuro-endocrine system. Such a concept advances measurably understanding of the clinical phenomena with which the practitioner who treats arthritis must deal. Under this interpretation, either great type of



arthritis can be seen, in part, as a series of sequential or related phenomena, expressive of known functions of the endocrine system which has, in some cases, exceeded, in others failed to achieve, its normal level of activity. No single major deviation seems to dominate the field and, at the outset, restoration of a balance under which the peripheral phenomena grow less or disappear is usually possible of demonstration.

The fact that later in the disease, when chronicity has supervened, such restitution is more difficult, should not be allowed to cloud the issue. Indeed, it not infrequently happens even in advanced cases that the same improved equilibrium can be achieved almost as easily. It is important to reiterate that control of such a situation cannot necessarily depend upon replacement therapy alone. Hyperactivity may also prevail and perhaps equally frequently.

The broad lesson taught by recital of the foregoing cases needs some further particularization. To discuss first hypertrophic or osteo-arthritis, it is clear from the cases cited by Hall and others,<sup>6</sup> as well as many in the writer's series, that "arthritis of the menopause" is amenable in a high percentage of instances to replacement therapy by means of estrogenic substances. The conclusion is unavoidable that a deficiency and imbalance in the endocrine field account essentially for the disease picture. It is equally clear that hypertrophic or osteo-arthritis, the pathologic name for "arthritis of the menopause," as illustrated in cases cited in the present text, is amenable to a therapeutic programme which centers around conditioned rest and correction of such physiologic burdens as may need adjustment, without resorting to any form of endocrine replacement therapy *per se*. The inference is equally inescapable in this second group cited that imbalance or deficiency accounts for the disease picture there also; certainly there is no justification for invoking another pathologic explanation for the same picture.

The corollary to this is that, even in the presence of a need for "replacement therapy," much the same results can be obtained by achieving an "equilibrium" between the several systems and endocrines concerned, even though replacement therapy *per se* be not administered. This is not to say that replacement therapy is to be omitted if indicated and available; it is to say, however, that even when it is available an "equilibrium" should equally be sought, since it is contributory to the same end and promotes better response to "specific" replacement.

Above and beyond these considerations, however, there is no assurance in this vexed field of the arthritides that we are dealing with single or specific deficiencies. The possibility must be entertained that several deficiencies exist or even, as just mentioned, that hyperactive states exist also. Indeed, such a condition of affairs is highly probable, and has been encountered in some cases of the writer's series as well as by other observers. Selye<sup>20</sup> concludes from his experimental work on animals that "the most prominent fact about the clinical syndrome of endocrine arthritis is that both hyperfunction

and hypofunction of several endocrine glands may elicit joint manifestations."

It is well recognized by students of endocrinology that the various endocrines bear active and often reciprocal relationships toward one another, such that dysfunction of one may have many and varied consequences elsewhere in the "chain." Without laboring further the possibilities involved here, it is plain that limitations to our knowledge of the number and kind of endocrinous dysfunctions, as well as limitations to the preparations available, justify emphasis upon any procedure which achieves the equilibrium above discussed. Indeed, such a course offers the only promise of bringing to bear influences upon a situation *so generic as to affect multiple imbalance*.

As already pointed out, the frequency with which such efforts meet with success is far from appreciated. They deserve wider use. Practiced rigidly in the way outlined, the therapy of arthritis teaches that the arthritic process is partly a reversible one, especially at the early stages, but to some extent also later in the disease, except for such gross pathologic changes as may have supervened.

Upon applying the principle of "achievement of equilibrium," just discussed, to *atrophic* or *rheumatoid* arthritis on the basis of the view that one is furthering a better balance within the neuro-endocrine chain and so affecting the bases of the disease, one is perhaps upon somewhat less secure ground. There is not, as yet, as much clinical evidence with which to incriminate the endocrine system in atrophic arthritis as in the case of the hypertrophic type. Nevertheless, evidence is not lacking as will be seen by reference to Table 1 and Case 3 (Mrs. E).

It is not justifiable as yet to say that atrophic arthritis stems chiefly out of a neuro-endocrine imbalance, but at the moment there appears to be no other explanation or hypothesis which so nearly accounts for the full picture.

In the present series, 3 cases of frank atrophic or rheumatoid arthritis have been selected, in 2 of which there was no clear-cut evidence of any single specific endocrine deficiency. There was consequently no clear indication for any specific replacement therapy. In the third case there was a lowered metabolic rate, and hormonal assay of the urine showed excessive production of one hormone and deficient production of two others. These several individuals were successfully treated upon much the same principle, viz., that of making less significant such inadequacies as might exist by means of decreasing the load upon them. From the purely clinical standpoint this is a logical corollary to replacement therapy, albeit not specific for any one deficiency. That it works in selected cases admits of no question, and it is probably influential in most cases when exhibited. On the other side of the picture it seems probable, as mentioned, that at times at least, hyperactivity exists in arthritis somewhere along the endocrine chain, analogous to the influence of the anterior pituitary on hypertrophic arthritis. Obviously no "subtraction" therapy is possible here, but it is entirely reasonable to suppose, in view of the known close interrelations of the major endocrines to each other, that a better equilibrium

between all or most of them would be a step towards restoration of normal function. It is in this connection that gentle sedation may be influential.

Translated into practical terms, the above considerations require the establishment of a regimen which must be followed rigidly and literally. To this end Table 3 was prepared, setting forth the order in which the above therapeutic steps can usually best be taken.

Referring to Paragraph 3 of Table 3, the amount of sedation required by these subjects is usually very small, if exhibited in conjunction with complete bed rest; and, indeed, with the whole programme. As little as gr.  $\frac{1}{4}$  phenobarbital, or some comparable sedative, q.i.d. will usually suffice, except perhaps on the first day or two. The fatigued state of which most arthritics complain will be greatly ameliorated in the same way by very small doses of tincture of nux vomica, as little as mm. 3, t.i.d.

By the term "optimal nutrition," Paragraph 4 of Table 3, is meant a diet which must vary with the individual but centers around an adequate though not excessive caloric intake, high protein content, ample "green" vegetables and fruits, ample fat and some restriction of the concentrated carbohydrate foodstuffs.<sup>9,16,22</sup> Again, the purpose in entering upon these details here is not to set forth a full therapy for chronic arthritis, which has been done elsewhere,<sup>14,15,23</sup> but to illustrate, in the light of the newer outlook upon the syndrome, the gratifying extent to which the simplest of procedures may initiate convalescence. Another reason for including Table 3 is to make clear that no single therapeutic measure is to be considered alone but only in conjunction with a broad-gauged and multi-faceted programme.

It is not to be supposed that the simple but effective foundation for further therapy, above discussed, will succeed equally well in all cases. Processes of recovery will usually be operative if given an opportunity but, obviously, the presence of massive infection, marked anemia, low plasma proteins, etc., may militate against recovery until corrected or improved. Clinical experience and sound judgment are as essential here as in any other major chapter of medicine, perhaps more than in most, as the brief discussion of the influences of rest and movement well illustrates. Mere titular familiarity with the physiologic aspects of rest, nutrition, exercise, physical therapy, etc., has wreaked havoc with hosts of arthritics. Anyone expecting a panacea in the physiologic approach discussed will be disappointed, and the object of emphasis upon it here is merely to make clear that such disturbances within the neuro-endocrine field as probably underlie the syndrome are often susceptible of correction by means of such an approach.

Another important corollary to the principle of "equilibration" of the arthritic derives from the unfortunate extent to which these sufferers are made the object of injections of various sorts, massive vitamin therapy and other more or less heroic measures. Although there is general agreement that procedures which elicit maximal reactions of the defense mechanisms of the body, such as fever, may have valuable consequences in certain disease states, such reactions have

not won routine acceptance for arthritics from critical students of the subject. Not only may these reactions fail to benefit the arthritic, they may, and often do, operate to postpone or completely prevent that "physiologic splinting" of the human unit which, of itself, may go a long way toward arresting the disease. This stricture has application also to the use of gold salts, notwithstanding the proven value of it to certain selected cases. It is indeed possible that this and many comparable agencies, alleged to be of value, often fail because of the unbalanced and improperly responsive condition of the host, not yet brought into optimal "alignment."

The syndrome of arthritis constitutes one of the best examples of so-called "psychosomatic medicine." The extent to which this background underlies the whole field of the arthritides is yet to be determined. In the light of recent developments, it is probable that undue emphasis has been placed upon separation of the so-called arthroses from the so-called true arthritides, since both apparently stem, in part at least, from the same stimuli and are largely amenable to the same therapy.

Given a situation in which the neuro-endocrine factors are avowedly many, and subject to varying emphasis, together with an equal number of precipitating or contributory factors, such as age, sex, anemia, infection, etc., one would expect the end picture to be varied. Indeed, Selye<sup>20</sup> concludes, from animal experimentation, "It appears quite possible that, depending upon the acuteness or chronicity of the condition or other incidental factors, the same etiologic agent may manifest itself in different ways and give rise to different types of arthritis."

**Summary.** 1. Increasing clinical experience and animal experimentation suggest that the ultimate nature of the rheumatic or arthritic process, at least so far as atrophic arthritis and hypertrophic arthritis are concerned, depends in part upon imbalance within the neuro-endocrine system.

2. This imbalance doubtless involves several links of the system rather than a single outstanding dislocation.

3. Clinical evidence suggests, as in most pathologic processes, that the early steps in such dislocations often permit of complete restitution by means of what may be called "physiologic splinting."

4. The basic means necessary to the above ends are relatively simple and center around a programme of conditioned rest and the achievement of an "equilibrium." Such measures should not be divorced, however, from that point of view toward the therapy of arthritis which envisages all departures from normal and considers all relevant and appropriate measures of treatment.

5. Some dislocations of the neuro-endocrine system permit or require "replacement therapy." On the other hand, many cases present no indications or justification for such measures. Some cases are apparently referable in part to overactivity.

6. In certain instances, of overactivity especially, though also in most others, mild sedation, under conditions of complete rest, will aid in restoring equilibrium.

7. With or without the use of "replacement therapy," the plan of

treatment discussed offers the only promise of bringing to bear influences upon the situation so generic as to affect multiple imbalance within the neuro-endocrine system.

8. Countless arthritics are open to great amelioration or arrest of the arthritic process through the application of physiologic principles which often appear too simple and obvious to deserve serious consideration.

9. Many cases of rheumatic disability in the Armed Forces in this country belong in some of the categories considered in this text. They doubtless represent a form of "laboratory experiment" induced by the war in young men not ordinarily exposed in large numbers to sustained pressure. It seems probable that therapy for some of them should include, when necessary, the principle of "physiologic splinting" discussed. Rigidity in carrying out this principle is usually essential.

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#### POLIOMYELITIS IN PREGNANCY

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DURING the epidemic of poliomyelitis in the fall of 1943, 6 women with poliomyelitis were admitted to our hospital, 4 of whom were

pregnant. Since the number of such cases in the literature is not great, a report of these cases seemed indicated, especially because of the ratio of the incidence in pregnant and non-pregnant women.

**Case Reports.** CASE 1. Mrs. L. C., aged 26, pregnant 2½ months, entered South View Hospital September 19, 1943, with the complaint of pain in the back and tenderness of the right lumbar area which began August 28, 1943.

Temperature on admission was 99.6° F. *Physical examination* revealed hyperesthesia of the right lumbar area, paralysis in the left iliopsoas, and right peroneal and tibialis muscles. There was spasm of the left and right hamstrings, and the patellar and Achilles reflexes were absent.

*Laboratory Findings.* Spinal fluid, 14 cells per c.mm.; 100% lymphocytes; smear, no bacteria; pellicle test negative for tubercle bacillus; dextrose, 62 mg. per 100 cc.; chlorides, 684 mg.; total protein, 67 mg.; globulin, faintly positive; gold sol, low tabetic curve; Kline and Kahn tests negative; culture, no growth in 48 hours. W.B.C. 8000; hemoglobin, 75%.

Treatment instituted the 1st hospital day and continued for 6 days, consisted of prostigmine, gr. 1/200, at 9 A.M. with hot fomentations applied to the entire body at 10 A.M. and 2 P.M. The patient was released on the 7th hospital day, with some spasm still present in the hamstring muscles bilaterally, weakness of the quadriceps bilaterally, and weakness of the right gastrocnemius and the extensors of the right foot. There was no complaint of tenderness at this time.

CASE 2. Mrs. E. J., aged 25, pregnant 4½ months, entered September 23, 1943, complaining of fever, vomiting and coryza for 2 previous days, and of stiffness of the neck with pains in the back on the day before admission.

*Physical examination* revealed a hyperirritable, hyperesthetic, stuporous, dehydrated female with severe respiratory distress. Arms and neck were flaccid, although some degree of voluntary control remained. Complete paralysis of the pharyngeal muscles of deglutition and partial paralysis of the intercostals, rectus capitis and right sternocleidomastoid were noted. Pupils were constricted and vertical nystagmus was present.

*Laboratory Findings.* Spinal fluid, pressure slightly increased; cells, 112 per c.mm.; differential: 98% lymphocytes and 2% neutrophils; dextrose, 67 mg. per 100 cc.; chlorides, 697 mg.; total protein, 44 mg.; Kahn and Kline tests negative; gold sol, low paretic curve; culture, no growth in 24 hours. Similar findings were reported on the following day.

The patient was given prostigmine, gr. 1/100, and atropine, gr. 1/150, on admission, and hot fomentations were applied to the neck and chest. She became comfortable for a short time, then a rapidly downward course ensued. Continuous oxygen was instituted and prostigmine repeated. Respirations became weaker, pulse rapid, and temperature elevated. Signs of consolidation were elicited in the left lung. The patient died on the 2nd hospital day. Cause of death was given as bulbar poliomyelitis with complicating terminal pneumonia.

CASE 3. Mrs. L. W., aged 21, pregnant 7 months, entered September 1, 1943. She had become ill on August 25, 1943, with headache, vomiting and fever. Headache persisted and on August 26 she complained of aching all over. On August 29, she experienced numbness and weakness in her arms with a similar condition developing in her legs 2 days later.

*Physical examination* revealed generalized tenderness with questionable hyperesthesia, spasm in the neck muscles, and a positive right Kernig's sign. Paralysis was present in both left and right wrists, especially on extension, in both elbows on extension and flexion, in both shoulders on elevation, and in both hips on flexion and abduction. Abdominal reflexes and the left patellar reflex were absent, but the Achilles reflexes were present. Abdominally a tumor of pregnancy of approximately 5½ to 6 months size was palpated. Fetal heart tones were heard slightly to the right of the midline. The presenting part was not palpated on rectal examination.

*Laboratory Findings.* W.B.C. 7200; R.B.C. 4.4 million. Spinal fluid: cells, 151 per c.mm.; 100% lymphocytes; sugar, 67 mg. per 100 cc.; chlorides, 677

mg.; globulin, faintly positive; gold sol, 1,122,100,000; and culture, no growth in 24 hours.

The patient was transferred to the Wisconsin General Hospital at Madison on September 14, at which time all but the plantar and wrist reflexes were absent, and a total quadriplegic paralysis was present except for slight flexion of the fingers of the right hand. There she received daily Kenny treatment and her gestation was closely followed. On October 16, 1943, because of a slowly rising blood pressure, labor was medically induced and a 5 pound 13½ ounce baby was delivered by breech extraction, completely normal except for a slight asphyxia possibly due to some prolapse of the cord.

CASE 4. Mrs. L. P., aged 32, was transferred to South View Hospital on September 9, 1943, from Milwaukee Hospital, where 3 days previously, she had delivered a full-term normal infant. She had become ill 7 days prior to admission with complaints of backache and pain in the left leg. The following day stiffness of the neck developed with increasing backache and leg pain, and upon admission she complained of pain in both lower extremities.

*Physical examination* revealed an apprehensive female with neck rigidity, spasm in the back muscle groups and sacrospinalis muscles bilaterally. Gross paralysis of the left leg and paresis of the right leg were present. Kernig's sign was elicited. The left patellar reflex was absent.

*Laboratory Findings.* Spinal fluid, clear; pressure normal, cells, 100 per c.mm.; dextrose, 47 mg. per 100 cc.; chlorides, 695 mg.; total proteins, 120 mg.; gold sol, negative; Kahn and Kline tests, negative.

Upon admission, routine postpartum care was immediately started. On the 2nd hospital day treatment was begun with prostigmine, gr. 1/200, and atropine, gr. 1/150, at 9 A.M. and application of hot foment to the lower extremities, body and neck at 10 A.M. and 2 P.M. This treatment was routine during the 17 days of hospitalization and she had no complaints referable to the therapy. The pain in the legs and the spasm of the back and neck muscles disappeared, while some spasm of the hamstring muscles remained.

**Discussion.** Poliomyelitis occurs infrequently in pregnancy. In his review in 1941, Aycock<sup>1</sup> found 28 reported cases of pregnancy complicated by poliomyelitis, and contributed another 28 cases from his personal records. A more recent review of the literature by Weaver and Steiner<sup>3</sup> lists 75 cases to which may be added the 2 of Harmon and Hoyne,<sup>6</sup> 3 described by Hürny<sup>7</sup> and 1 by Biermann and Piszczek.<sup>3</sup> These, with our cases, bring the total reported to 85.

In an experimental study of pregnancy and poliomyelitis, Weaver and Steiner<sup>3</sup> report that 3 of 13 cotton rats, inoculated during the first trimester of pregnancy, resisted infection with poliomyelitis virus. All animals inoculated in the second and third trimester as well as all virgin animals were uniformly susceptible. Furthermore, the incidence of poliomyelitis in the 75 human cases cited by these authors when divided into trimesters is as follows: first trimester, 17.1%; second trimester, 34.3%; and third trimester, 48.6%. Weaver and Steiner feel, then, that their results indicate a significant increase in resistance to poliomyelitis in early pregnancy over the later months of pregnancy and over the non-pregnant state.

The following analysis of the clinical data would not seem to support the latter conclusion. Brahdy and Lenarsky,<sup>4</sup> using the data from the 1931 epidemic, reported 1010 cases of poliomyelitis at the Willard Parker Hospital, 30 of which were over the age of 19. Of the 30 cases, 15 were women and 3 of them were pregnant (20%). Aycock<sup>1</sup> included a personal communication from Vaughan regarding 528 polio-

myelitis cases in Detroit (1939), 255 of whom were paralytic. Eleven of the female paralyzed cases were over the age of 21, and 3 of these women developed the disease during pregnancy (27.3%). In our 1943 series, there were 41 cases of poliomyelitis at the Milwaukee Isolation Hospital, 9 of which were over 19 years of age. Of these 9 cases, 6 were females, 4 of whom were pregnant (66.7%). These experiences suggest, then, that pregnancy may increase rather than decrease a woman's susceptibility to poliomyelitis.

Before discussing further the relation of pregnancy to susceptibility to poliomyelitis, it might be well to comment on the studies of Draper.<sup>5</sup> He was the first to attempt a correlation between morphologic characteristics and incidence of the disease, describing a "poliomyelitic type." After anthropometric studies of the face, jaws, teeth, interpupillary space, hand index, biiliac-biacromial diameter ratio, etc., he concluded that persons susceptible to the virus of poliomyelitis are of a special constitutional type which differs from that of non-susceptible individuals.

Aycock<sup>2</sup> regarded the correlation between the poliomyelitis type of Draper and the findings of his anthropometric studies as indicative of an imbalanced or inefficient endocrine system. He studied this problem by castrating a group of female monkeys and injecting them, along with normal controls, with poliomyelitis virus. Some of the castrated monkeys were first prepared by receiving a course of estrogen therapy. There was a significant difference in susceptibility to poliomyelitis in the non-estrogen prepared monkeys as compared with the estrogen prepared animals, the latter group proving more resistant. He further concluded that the injection of estrogenic material into castrated female monkeys enhanced their resistance to the virus and delayed the onset of the disease in those who were destined for infection. Other experiments, in which comparative urinary estrogen assays were done on chronic poliomyelitic patients and control individuals, revealed a higher average estrogen content in the urine of poliomyelitis patients. Although he mentions the possibility that this finding might be a sequela rather than a contributing factor, he was inclined to think, in view of epidemiologic considerations, that the outpouring of the estrogens is a reflection of a physiologic condition which had been present before the onset of the disease. Such a physiologic character of the increased susceptibility to poliomyelitis is further borne out by its seasonal occurrence, climatic variations, and constitutional specificity.

Both the work of Draper and that of Aycock, therefore, support the theory that the endocrines can influence resistance or the susceptibility to anterior poliomyelitis. With pregnancy, ovarian function is increased with resulting rise in estrogen and progesterone levels together with the appearance of a hormone, gonadotropin. Thus one might wonder whether the changed concentration of estrogens in pregnancy might increase the susceptibility of the gravid woman to the disease.

It is possible, too, that other changes than those in the gonads are



concerned, *i. e.*, in the pituitary or in the whole endocrine system, since all the glands of internal secretion are so closely interrelated. One might even speculate as to the effect of fetal endocrine secretion on the mother. The possible rôle of the thymus, if we may call it a gland, is particularly intriguing. It develops rapidly in the fetus, and in postnatal life its period of greatest development closely parallels maximum susceptibility to poliomyelitis.

Whatever the true mechanism of resistance to poliomyelitis may be, this concept of a relation between altered endocrine function in pregnancy and increased susceptibility, is an interesting approach to the problem generally and seems to us to merit further study. Suggested avenues of investigation are: (1) the occurrence of the symptoms and signs of the disease in relation to the menstrual cycle; (2) the effect of estrogens on the course of the acute disease in humans (both pregnant and non-pregnant); (3) an assay of urinary estrogens in the acute poliomyelitic pregnant and non-pregnant female; (4) studies of the thymus gland in poliomyelitic women, both pregnant and non-pregnant, by Roentgen ray and postmortem examination; (5) comparison of thymic tissue and thymic extract in pregnant and non-pregnant women; (6) effect of fetal monkey thymic extract on the susceptibility of thymectomized female monkeys subjected to the virus of poliomyelitis; (7) effect of fetal thymus extract on estrogenic production by assay of urinary estrogens.

There was no evidence of poliomyelitis in the 2 living babies born of 2 of the poliomyelitis cases described, nor was the fetus of the 1 mother dying of the disease affected. These observations agree with those of most other workers who find that poliomyelitis is not transmitted from the mother to the fetus *in utero*.<sup>2,3,4,5,6</sup>

**Summary.** 1. Case histories are presented of 4 pregnant women who developed anterior poliomyelitis.

2. The high incidence of pregnant women among adult females contracting the disease leads to the conclusion that pregnancy increases susceptibility to poliomyelitis. In our series, 4 out of 6 poliomyelitic women were pregnant; Aycock mentioned 3 out of 11 cases; and Brahdy and Lenarsky presented 3 pregnancies in 15 cases, making a total of 10 pregnant women among 32 adult females. Thus 31.3% of these poliomyelitis cases were pregnant. It is thought that this figure is minimal, since the result is based on the incidence of pregnancy and poliomyelitis in all female adult poliomyelitics, including those not married.

3. Evidence has been summarized which suggests that the increased susceptibility to the disease in pregnancy may possibly be due to the change in ovarian secretion at that time, although pituitary dysfunction and fetal hormones upsetting the mother's balance may also be suspected.

4. In the 4 cases of poliomyelitis complicating pregnancy at the Milwaukee Isolation Hospital, delivery of 2 normal children, and examination of 1 fetus in a dead mother, confirmed the opinion that

poliomyelitis in the mother has not affected the newborn child, nor does it hamper normal spontaneous delivery.

5. Possible studies on the endocrinologic approach to poliomyelitis are suggested.

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# PROGRESS OF MEDICAL SCIENCE

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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### THE RELATION OF STREPTOCOCCI TO HUMAN DISEASE: IMPORTANCE OF IDENTIFICATION AND NOMENCLATURE

#### II. STREPTOCOCCI OTHER THAN THOSE OF GROUP A

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ALTHOUGH the more acute and severe streptococcal infections of man are usually due to the beta hemolytic streptococci of Lancefield's serologic Group A, as related in Part I of this review,<sup>7</sup> it is now recognized that there are many sporadic cases of infection by those of Groups B, C, D, F and G. Cultural differences among the streptococci of these groups began to be recognized before they were differentiated serologically and helped to explain many anomalous clinical results, difficult to understand when all of these streptococci were reported as *Streptococcus hemolyticus*. Nevertheless, serologic grouping by the precipitin method of Lancefield<sup>17</sup> or its technical modifications<sup>5</sup> not only saves time but also indicates antigenic relationships between different species of streptococci. It appears that all members of a species of streptococcus belong to a single serologic "group" but that more than one species, as determined by cultural study, may exist within each group. The groups may also be subdivided into a number of serologic "types" by precipitation or agglutination. The types do not always coincide with species and there may be a number of different types within a single species. The determination of type is very useful for tracing sources of infection or mode of contagion. For better understanding of the pathology, epidemiology and therapy of streptococcus infections it is desirable that the serologic group, the species and the serologic type of each strain shall be determined.

The beta hemolytic streptococci of serologic Group B usually produce double zones of hemolysis about deep colonies in blood agar plates when cultivated and observed under favorable conditions (Brown, 1937<sup>4</sup>). Since the initial zone of hemolysis is usually small with poorly defined

periphery, it may be mistaken for the alpha prime appearance, as was done by Hansen, Hucker and Snyder,<sup>15</sup> unless it is studied in optical section under the 16 mm. objective of the microscope.\* The Group B hemolytic streptococci characteristically hydrolyze sodium hippurate and ferment trehalose but not sorbitol. They may be subdivided according to source and fermentation of lactose and salicin (Table 2).

TABLE 2.—GROUP B HEMOLYTIC STREPTOCOCCI DIVIDED ACCORDING TO SOURCE AND FERMENTATION OF LACTOSE AND SALICIN

Species	Source	Fermentation of		Prevalence† at Johns Hopkins Hospital
		Lact.	Sal.	
I. <i>S. opportunus</i> Brown 1939 . . . . .	Human	—	+	26 strains
II. Not named . . . . .	Human	+	+	22 "
III. <i>S. mastitidis</i> Guillebeau 1890 . . . . . ( <i>em.</i> Frost and Engelbrecht 1940)	Bovine	+	+	
IV. <i>S. asalignus</i> Frost, Gumm and Thomas 1927 . . . . .	Bovine	+	—	1 strain

Apparently these closely related species are entities and it is convenient to refer to them by names. *Streptococcus opportunus* is found frequently in the normal human throat and vagina. It may assume the rôle of an opportunist pathogen, producing infections in various parts of the body and rarely fatal septicemia. Usually the source of such infections may be traced to the throat or genito-urinary tract of the patient. Group B hemolytic streptococci fermenting both lactose and salicin may also be found in the human throat and vagina and have the same pathogenic significance as does *S. opportunus*. The lactose +, salicin + strains from human sources are culturally similar to *S. mastitidis* which is one of the most common causes of bovine mastitis but there is some evidence that they are not identical. Brown,<sup>6</sup> confirmed by Simmons and Keogh,<sup>21</sup> found the human strains more pathogenic for mice than were the bovine strains. The latter authors also found the human and bovine strains to belong to different serologic types within Group B. This appears the more significant since the human strains were from persons not associated with the cows or milk from which the bovine strains were obtained. *S. asalignus* also is a common cause of mastitis and has been found by Frost and Engelbrecht<sup>14</sup> in the throats of milkers, and by Plummer<sup>19</sup> in the throats of children consuming infected milk. It has not been reported from the human genito-urinary tract. At one autopsy we isolated it from the heart blood, lung and spinal fluid of a child who died of lead poisoning and whose lungs showed evidence of aspiration of food or vomitus. Frost and Engelbrecht also report the frequent presence of *S. mastitidis* in the throats of milkers. It is obvious that such persons may act as transient carriers of *S. mastitidis* and *S. asalignus* without suffering ill-effects and that the former organism is indistinguishable culturally from the lactose +, salicin +, Group B hemolytic streptococcus found in the throats, genito-urinary tracts and occasional lesions of persons not exposed to mastitis milk. While there is no evidence that the bovine strains are pathogenic for man, Little<sup>18</sup> has shown that mastitis may be produced by the injection of human strains into the bovine udder. As is the case with *S. pyogenes*, it may be that occasionally a cow is accidentally infected by a careless

\* For the recognition of alpha and beta zones microscopic study of deep colonies is essential. The study of surface colonies only is unsatisfactory.<sup>13</sup>

† Strains from 2349 autopsies from which culture material was taken during a 6-year period.

milker. There is no evidence that Group B streptococci are of epidemic significance. Of 1070 strains of streptococci from urine specimens of patients in the gynecologic and obstetrical services of Johns Hopkins Hospital, 6% were Group B beta hemolytic streptococci. Of 232 strains of streptococci from the uteri of patients with febrile puerpera, only 3 were Group B strains.

Similar to *S. mastitidis*, except that it produces alpha zones in blood agar, is *S. agalactiæ* Lehmann and Neumann 1896 (*em.* Frost and Engelbrecht 1940). It belongs to serologic Group B and is a common cause of bovine mastitis. It has not been found in human disease nor reported from the human throat although there is no apparent reason why it should not occur there as a transient.

Beta hemolytic streptococci of serologic Group C may produce disease in man and other animals. Some may be harbored by the normal human throat and vagina. The known species are listed in Table 3.

*S. zoëpidemicus*\* is appropriately described as "the animal pyogenes"; among animals it plays a rôle similar to that of *S. pyogenes* among men. Although it has been found in the throats of persons in close association with animals<sup>14</sup> it is doubtful whether it is pathogenic for man. Until the differential value of trehalose and sorbitol was recognized and serologic grouping was employed it could not be distinguished from *S. pyogenes*.<sup>8,9,10</sup> *S. equi* has long been known as the cause of "strangles," a cervical adenitis of horses. There is no reason to believe that it is pathogenic for man. *S. equisimilis* has been found in infections of various animals (man, cow, horse, monkey, chicken) and in the normal human throat and vagina. Evans<sup>11</sup> summarizes evidence of the transmission of the infection from horses to man. Because of similar bacteriophage sensitivity she regards those strains which fail to ferment salicin or ferment lactose (IV and V in Table 3) as subgroups of *S. equisimilis*. Human infection by Group C hemolytic streptococci may be local or systemic, mild or severe, sometimes fatal. About 200 strains reported in the literature came from such sources as puerperal sepsis, erysipelas, scarlet fever, hemorrhagic smallpox, mastoiditis, sinusitis, otitis, urinary tract infections, pneumonia, septicemia, abscesses and ulcers in various parts of the body. As compared with Group A streptococcus infections there have been relatively few cases of sore throat and no outbreak of epidemic proportions.

*S. dysgalactiæ* Diernhofer 1932 (*em.* Little 1939), a cause of bovine mastitis, produces alpha zones in blood agar and is a member of serologic Group C. It has not been reported from human sources.

The streptococci of serologic Group D are collectively known as enterococci (Sherman, 1937<sup>20</sup>). Their normal habitat is the intestine of man and many other animals. Like many other bacteria in the intestine they may cause disease by extension or conveyance from the intestine to susceptible tissues or organs. They are not highly virulent but are more resistant to heat, disinfectants and drugs than are other streptococci. In stained smears they often appear as slightly elongated or oval Gram-positive cocci in pairs rather than in chains, and, in stained sections of tissue, may be mistaken for pneumococci. The known species encountered in human infections are listed in Table 4.

The enterococci account for nearly 50% of the streptococci isolated from autopsy material (Table 5); the beta hemolytic species, about 7%, and the alpha species, about 40%. About three-quarters of them were from heart

\* The name appears to be valid although one might wish that it had been *epizoölicus*.

TABLE 3.—BETA HEMOLYTIC STREPTOCOCCI OF SEROLOGIC GROUP C

Species	Lact.	Sal.	Mann.	Treh.	Sorb.	Fib.*	Prevalence† at Johns Hopkins Hospital
I. <i>S. zoëpidemicus</i> Frost and Engelbrecht 1935	+	+	—	—	+	—	
II. <i>S. equi</i> Sand and Jensen 1888 ( <i>em.</i> Evans 1936)	—	+	—	—	—	—	
III. <i>S. equisimilis</i> Frost and Engelbrecht 1940	—	+	—	+	—	(+)	4 strains
IV. } IV and V are regarded by Evans† as subdivisions of <i>S. equisimilis</i>	{ —	—	—	+	—	..	3 "
V. }		—	—	+	—	..	2 "
VI. Others		+	±	±	±	..	3 "

\* Lysis of human fibrin.

† See note under Table 2.

(+) Strains from human sources positive.

± Positive or negative.

TABLE 4.—STREPTOCOCCI OF SEROLOGIC GROUP D

Species	Bld. ag.	Prot.*	Lact.	Sal.	Mann.	Treh.	Sorb.	Prevalence† at Johns Hopkins Hospital
I. <i>S. zymogenes</i> MacCallum and Hastings 1899 ( <i>em.</i> Sherman 1937)	Beta	+	+	+	+	+	+	6 strains
II. <i>S. durans</i> ( <i>syn. hemothermophilus</i> Sherman and Wing 1935, 1937)	Beta	—	+	(+)	(—)	(+)	—	1 strain
III. Not named (possibly a variant of <i>S. zymogenes</i> )	Beta	—	+	+	+	+	+	46 strains
IV. <i>S. liquefaciens</i> Sternberg 1893 ( <i>em.</i> Orla-Jensen 1919)	Alpha	+	+	+	+	+	+	15 "
V. <i>S. fecalis</i> Andrewes and Horder 1906	Gamma to alpha	—	+	+	+	+	+	318 "

\* Liquefying gelatin and coagulated serum.

† See note under Table 2.

(+) or (—) Usually + or — according to Sherman, 1937.

blood, lungs and peritoneum, named in the order of occurrence. Doubtless many of these isolations were due to postmortem invasion but there were also cases of enterococcus endocarditis, bacteremia, peritonitis, and mixed culture pneumonia as well as many local infections. Infection of the urinary tract is frequent. Of 1070 strains of streptococci from urine specimens of patients on the gynecologic and obstetrical services of the hospital, about 58% were enterococci, whereas of 232 strains from uteri of patients with febrile puerpera, only 9% were enterococci, none of which was hemolytic. Of 53 beta hemolytic enterococci from autopsy material, 6 were *S. zymogenes*, 1 *S. durans*, and 46 a streptococcus resembling *S. zymogenes* except that it failed to liquefy gelatin or coagulated serum (Species III, Table 4).

TABLE 5.—RELATIVE PREVALENCE OF VARIOUS STREPTOCOCCI

	Urine cultures from gynecology and obstetrics	Uterine cultures from febrile puerperæ	Autopsy cultures
Aerobic . . . . .	98.4%	24.5%	98.0%
Beta . . . . .	12.4	2.6	31.4
Group A . . . . .	0.4	0.9	14.5
Group B . . . . .	6.0	1.3	6.2
Group C . . . . .	1.3	0.4	1.5
Group D . . . . .	3.7	..	7.3
Other than A, B, C or D . . . . .	1.0	..	1.9
Alpha . . . . .	83.2	19.3	66.0
Enterococci, Group D . . . . .	54.0	9.0	40.0
Other alpha strep. . . . .	29.2	10.3	26.0
Gamma . . . . .	2.8	2.6	
Anaerobic . . . . .	1.6	69.0	1.5
Beta . . . . .	0.1	22.4	1.5
Alpha . . . . .	0.2	10.1	
Gamma . . . . .	1.3	36.5	Few
Micro-aerophilic . . . . .	..	6.5	0.4
Beta . . . . .	..	3.0	0.4
Alpha . . . . .	..	1.7	
Gamma . . . . .	..	1.8	

The streptococci of serologic Group E are not known to be pathogenic for man. The known strains have been from cows' udders showing little or no evidence of mastitis.

During a period of 6 years we have obtained from autopsy material 3 strains of Group F (2 from lungs and 1 from peritoneum) and 4 strains of Group G (3 from lungs and 1 from heart blood) beta hemolytic streptococci. Among the latter none was *S. anginosus*. Two other strains resembled those of Group G culturally and did not belong to Groups A, B, C or D but no G serum was available at the time. Obviously there are not enough strains of Groups F and G to warrant any other conclusion than that they have been found rarely in our autopsy material.

Although the alpha enterococci belong to serologic Group D and certain alpha mastitis streptococci belong to Groups B and C, most of the so-called "viridans" streptococci of human origin do not belong to any of Lancefield's serologic groups. These occupy a very prominent place in throat cultures, are found in all normal throats, and so it is difficult to ascribe any significance to them when found there. They are opportunist pathogens and our appraisal of them must be derived from their presence in pathologic lesions, the blood stream, the urine, or the uterus when there is clinical evidence of infection. The species commonly encountered are listed in Table 6.

TABLE 6.—VIRIDANS STREPTOCOCCI

Species	Lact.	Sal.	Mann.	Milk*	Prevalence† at Johns Hopkins Hospital
I. <i>S. mitis</i> Andrewes and Horder 1906. (em. Holman 1916)	+	+	—	—	97 strains
II. <i>S. salivarius</i> Andrewes and Horder 1906	+	—	—	+	41 “
III. <i>S. ignavus</i> Holman 1916	—	—	—	—	39 “
IV. <i>S. equinus</i> Andrewes and Horder 1906	—	+	—	—	22 “

\* Coagulation of milk.

† See note under Table 2.

It is not to be assumed that lactose, salicin, mannitol and milk are the only test substances required to diagnose these species. They have the other differential characteristics of the “viridans division” listed in Sherman’s Table 1.<sup>20</sup> In Sherman’s Table 3 *S. mitis* is included with *S. salivarius* and *S. ignavus* with *S. equinus* by indicating salicin fermentation as  $\pm$ . We do not find  $\pm$  signs of much differential value and, since we have no evidence that the salicin fermentation is variable, prefer to give different names to these streptococci. We have found *S. mitis* about twice as frequently as *S. salivarius*, and *S. ignavus* more frequently than *S. equinus* (Table 6). We notice no difference in the distribution or localization of these species in autopsy material; most of the strains are from lungs and heart blood. Endocarditis may be caused by any of them or by enterococci. These 4 species of viridans streptococci comprise about 26% of streptococci from autopsy material, 29% from urine specimens and 10% from uteri (Table 5).

Reasons similar to those which we urged against the use of the name *S. hemolyticus*<sup>7</sup> influence us to disapprove of the name *S. viridans*. These names are too broad to be used in a specific sense. There are too many hemolytic streptococci and too many viridans (green-producing) streptococci for inclusion in single species. We shall learn more about drug therapy when we cease to read reports of *S. viridans* endocarditis treated successfully (or unsuccessfully) with so-and-so.

The streptococci which produce the gamma appearance in blood agar (neither hemolysis nor greenish discoloration about deep colonies<sup>3</sup>) are negligible in our autopsy series and comprise less than 3% of the streptococci from urines and uteri. This may be due to several causes. Differences in the basic agar and the species of blood used are factors. In some laboratories it is not customary to incubate blood agar plates for 48 hours and then reexamine them after refrigeration overnight; some alpha zones are not apparent until after refrigeration. This is notably true of some strains of *S. fecalis* and has led Topley and Wilson<sup>22</sup> to describe their appearance as gamma rather than alpha; actually in 24 hours the deep colonies of *S. fecalis* are likely to appear as gamma and later as alpha.

The anaerobic and micro-aerophilic streptococci remain to be discussed. The largest incidence of anaerobic streptococci is to be found in uterine cultures (69%) (see also Harris and Brown<sup>16</sup>). It appears that all streptococci grow well anaerobically. This has led some workers to incubate all primary cultures anaerobically and is not bad practice provided later attempts are made to cultivate the isolated streptococci aerobically. Some streptococci which require anaerobic conditions for isolation soon acquire the ability to grow aerobically and so are not true anaerobes. Under anaerobic conditions the alpha appearance may be suppressed, resulting in either the beta or gamma appearance.<sup>3</sup> It may be for this reason that the incidence of anaerobic alpha strains among our uterine cultures is relatively small (10%). In this laboratory Brewer’s thiogly-



collate medium<sup>2</sup> has been found excellent as an enrichment medium for all streptococci.<sup>12</sup> When pathologic material is inoculated into this medium both anaerobic and aerobic streptococci are isolated more frequently than by primary plating in blood agar although the latter is also advisable in order to obtain relative counts of the number of bacteria present in the original material. In our autopsy and urine series of cultures the anaerobic and micro-aerophilic strains comprise less than 2% of the streptococci and we can attach no special significance to them.

Since the year 1938 the sulfonamides have been used extensively for the treatment of streptococcus infections at the Johns Hopkins Hospital. In the same year we started grouping all beta hemolytic streptococci isolated from autopsy material. In the culture records for the years 1932 to 1938 we are able to recognize almost all of the strains of Groups A, B, D, those of Group C which we described as "equi-like" (now called *S. equisimilis*), and a few others which probably did not belong to any of the above groups. In Table 7 is an enumeration of the strains isolated during these two 6-year periods from autopsy material.

TABLE 7.—STRAINS OF BETA HEMOLYTIC STREPTOCOCCI ISOLATED FROM  
AUTOPSY MATERIAL

	Group A	B	C	D	Others
1932-1938 . . . .	190	42	29	40	12
1938-1944 . . . .	112	49	12	55	18

There appears a marked decrease in the number of strains of Group A, most of them *S. pyogenes*. If the numbers are significant there is also a decrease from 29 to 12 in the incidence of Group C streptococci but it is possible that some of those listed for 1932-1938 may have been of Groups F, G or H. The incidence of streptococci of Groups B and D shows no significant change. It may be that these figures support what we find to be the opinion of clinicians; that sulfonamide therapy is of greatest value in the treatment of Group A streptococcus infections, of no value for Group D infections, and of questionable value for infections by streptococci of other groups. These opinions are supported by the experimental results of Bliss, Long and Feinstone.<sup>1</sup> There is an impression that the sulfonamides are of some value in the treatment of urinary tract infections by Group B streptococci. Our data do not permit any opinion as to the value of sulfonamides in infections by other than the beta hemolytic streptococci. Only by a correlation of more exact systematic bacteriology with clinical observation can this information be obtained.

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## PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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SEASONAL PREVALENCE AS A PRINCIPLE IN  
EPIDEMIOLOGY

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BACTERIOLOGIC methods for the detection of infectious agents in the determination of infectious periods of disease, the establishment of sub-clinical infection, healthy carriers or other sources of infection, and immunity tests for surveying previous infection are now in common use in epidemiology. Knowledge of the epidemiology of many infectious diseases has been gained very largely, if not entirely, from the use of these precise methods. In some diseases, laboratory procedures of this kind have served more to verify or clearly define concepts already arrived at by the older method of deduction and inference from observation of the distributional features of disease. In others, their use has been responsible for the amendment or rejection of erroneous hypotheses which had been based on studies of the distribution of the disease alone. In still others not amenable to such techniques for one reason or another, the older method of inference and analogy must still be relied upon, and, when properly used as a tool in epidemiology, does not necessarily carry a risk of error greater than that which exists in the experimental method. At any rate, it serves to eliminate large numbers of unlikely hypotheses and to aim experimental approaches toward a limited number amongst which the right one is to be found. There are many examples of the successful use of the inferential method: Budd's conception of typhoid fever—including chronic carriage, the presence of the infecting agent in intestinal discharges and its transmission through contaminated water supplies—developed from his observations of the distribution of the disease in rural areas long before the discovery of the typhoid bacillus, was later to be abundantly confirmed by the newer methods. But the great development of the experimental method has thrown the older method into the shadow. As Theobald Smith<sup>24</sup> said, "The latter looks at things in nature, describes and compares them, and deduces from such comparisons certain underlying concepts. The experimental method takes the same phenomenon and tries to check or limit all but one of the activities entering into it so that this one activity can be observed, recorded, measured, and weighed. . . . Both methods have their special advantages and disadvantages." When we witness some of the broad epidemiologic generalizations drawn from isolated experimental findings we cannot but be reminded of Theo-

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bald Smith's further statements that "the experimental method must not let too many machines get between it and the whole and must find some way of putting the fragment surgically removed for experimental purposes back into the whole" and that "the comparative method is frequently in position to restrain the generalizations deduced from experimental procedures and to keep the experimenter from steering away from the goal, which is an understanding of the totality."

The mode of spread of the infectious agent has been the central idea in epidemiology. Inferences, both from experimental findings and from various distributional features of disease, have tended to be directed toward mode of spread—the actual mechanics of transfer of the microbial agent from one to another. Good reason for this emphasis on mode of spread lies in the fact that in many diseases it not only is the important determinant, but also offers a point of attack in practical control. But that it has been stressed at the expense of consideration of other factors which act as major determinants is well expressed in the writings of an earlier period before microbiology had gained the ascendancy. In 1750 John Huxham<sup>15</sup> wrote, "The highly putrid, malignant Fevers many Times arise from mere antecedent Acrimony of the blood . . . yet generally the pestilential and petechial have their Origin from Contagion; and may therefore affect Persons of all Constitutions, which will of Course produce a great Diversity of Symptoms . . . For, as the received Contagion acts nearly in the same Manner as Acrimony, it will have very different Effects, when it invades a strong vigorous Constitution . . . from what it will, when it attacks a weak, lax Habit . . ." And when he speaks "Of the Power of the Winds and Seasons in producing these Distempers" and describes their effects on the body (fluids and solids) together with what might be called his experimental observation that "It is Fact, that *cæteris paribus*, Blood drawn, in such prevailing Constitutions of the Atmosphere, is constantly found more dense and viscid than in long moist warm Seasons," he evidently was no less sure of his epidemiologic inferences—seasonal variation in constitution—than we are today when we attribute seasonal variation in infectious disease exclusively to seasonal variation in mode of spread.

Seasonal fluctuation is not only a very general epidemiologic principle, but for a given disease is one of its most constant epidemiologic characteristics. Most infectious diseases exhibit marked variations with season and these are remarkably constant from year to year. The influence of season is most strikingly evident in the variation in seasonal curves at different latitudes amounting to a complete reversal of months of prevalence in corresponding latitudes in the northern and southern hemispheres.

The constancy of seasonal prevalence of disease has made it a favorite basis for epidemiologic inference. In a number of diseases it is clear that seasonal variation is determined by corresponding changes in the opportunities for transmission of the infectious agent (as influenced by the bionomics of the vector). This unmistakable association between mode of spread and season in certain diseases has been generalized into a law of seasonal prevalence which has, in turn, led to the grouping of diseases with reference to modes of spread on the basis of their seasonal prevalence alone. As Madsen<sup>21</sup> has pointed out, "Des l'antiquité, on s'est rendu compte que les maladies présentaient une intensité variable selon les saisons. Hippocrate distinguait déjà entre les maladies hivernales et printanières, d'une part et les maladies estivales et automnales d'autre part." One of the most sweeping applications of this "law" of seasonal

prevalence is the doctrine to the effect that infections transmitted through the upper respiratory tract are all winter diseases because of a hypothesized increased transmission resulting from the "closer crowding" of winter; and the converse that a disease not exhibiting a similar seasonal prevalence must have a different mode of spread. This has been emphasized in a very recent paper by Wells<sup>41</sup> in the statements that: "The concentration of microorganisms in the air is an equilibrium between the rate of addition and rate of elimination, the latter being determined primarily by ventilation . . . . In those localities where there is a marked difference between summer and winter temperatures, incidence of infection (and of the disease where the two are synonymous, as in the case of measles and chickenpox) will likewise show a marked sensitivity to seasonal change. . . ." And finally, "Seasonal patterns will vary with climate, since this affects the length of the season when ventilation is impeded by closed windows." However, the seasonal curves of upper respiratory disease in northern and southern latitudes do not always bear out these assertions without the assumption of differences in such factors as rate of accumulation of susceptibles.

Insect-borne diseases for the most part come under a generalization of summer prevalence, but even here there is a striking exception—typhus fever. If one argued the mode of spread of typhus fever on the basis of seasonal prevalence alone, according to the doctrine so rigidly adhered to in diseases grouped as upper respiratory (forgetting all established facts concerning the louse and its habits), an inference that typhus is insect-borne would hardly be made. Such a situation, now highly imaginary of course, actually existed in 1814 when Hildenbrand wrote, "The source of all typhus matter is to be looked for solely in concentrated human effluvia." This was still quoted by Hirsch<sup>13</sup> in 1883 who added the idea that "overcrowding in filthy and unventilated rooms affords the essential condition for the development of typhus-foci, and for the spread of the disease. . . . The diffusion of the disease, or the conveyance of the morbid poison, takes place equally by the air surrounding the patient, as by personal intercourse and by objects—healthy men or things—which become carriers of the poison that clings to them."

The essential point in the present connection is that no one would now question the insect transmission of epidemic typhus because it is not a disease of summer prevalence as are most of the insect-borne diseases. But the establishment of the exception to the rule in the case of typhus, a member of the group of diseases in which the mechanism of seasonal fluctuation is better understood, seemingly has not yet opened in the minds of many the possibility of exceptions in the infections transmitted directly from man to man. In this group where, after all, the exact mechanism which determines seasonal prevalence is still conjectural, there is still insistence that all members of the group should conform to the majority pattern of seasonal prevalence. In both insect-borne and contact disease groups, epidemiologic activity represents the interplay of parasite, environment and host. The discrepancy in understanding of the two groups in respect to mechanics of transmission doubtless lies in part to the fact that in the former, all but one of the activities can be checked or limited so that this one can be observed—particularly true of the environmental factor in disease in which intermediary sources of infection are involved. In the latter group in which transmission is directly from man to man, the activities of parasite, environment and host are so closely inbound that one cannot be "surgically removed" for experimental pur-

poses and then put back into the whole, in the Theobald Smith sense. As Madsen<sup>21</sup> pointed out, "Pour un groupe important de maladies, celles que transmettent les insectes, l'action des saisons semble facilement explicable; il existe un parallélisme entre les fluctuations saisonnières de ces maladies et les fluctuations correspondantes de la vie des insectes, entre la périodicité de la peste, du typhus exanthématique, du paludisme, et le rythme vital de la puce, du pou, du moustique." And yet season is no common denominator of disease, for the same disease, having more than one mode of spread, may exhibit different seasonal curves, distinguishing each of its modes of spread. In tularemia, 4 seasonal curves can be distinguished dependent on whether it is transmitted by the ticks *D. andersoni*, *D. variabilis*, the horsefly *Chrysops discalis* or directly from rabbit to man (Chart 1). Even in this group of diseases where seasonal preva-

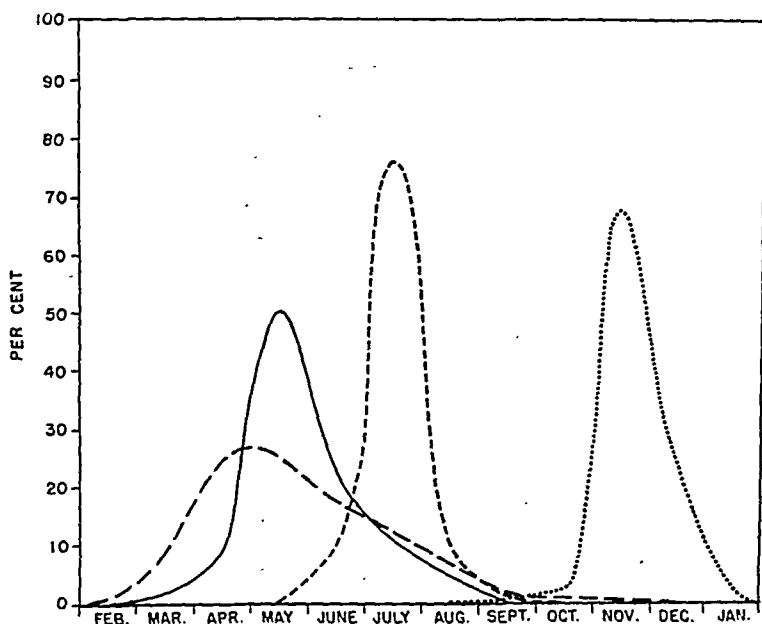


CHART 1.—Seasonal prevalence of tularemia. (Schematic.) Transmitted by: *D. andersoni* ———; *D. variabilis* ———; *Chrysops discalis* ———; rabbit contact ———. (Data from Pub. Health Rep., 52, 107, 1937.)

lence can be so closely associated with variation in the frequency of transmission, it might be stated, although the point is academic rather than practical, that seasonal prevalence may be due in the strict sense to seasonal variation in the virus reservoir rather than to seasonal variation in the actual mechanism of transfer from the insect to man. Outbreaks of malaria, for example, have occurred in midwinter, where opportunities were provided for the maintenance of mosquito reservoirs in indoor cisterns.

Although as Madsen said, the action of season in the group of insect-borne diseases seems easily explainable, the action of season on the upper respiratory infections, on the other hand, does not seem so easily explainable when the question is carried beyond the simple generalization that this group of diseases—herd or crowd diseases—is influenced by seasonal differences in crowding in summer and winter, which, in turn, affect the

ease with which their infectious agents are transferred from person to person.

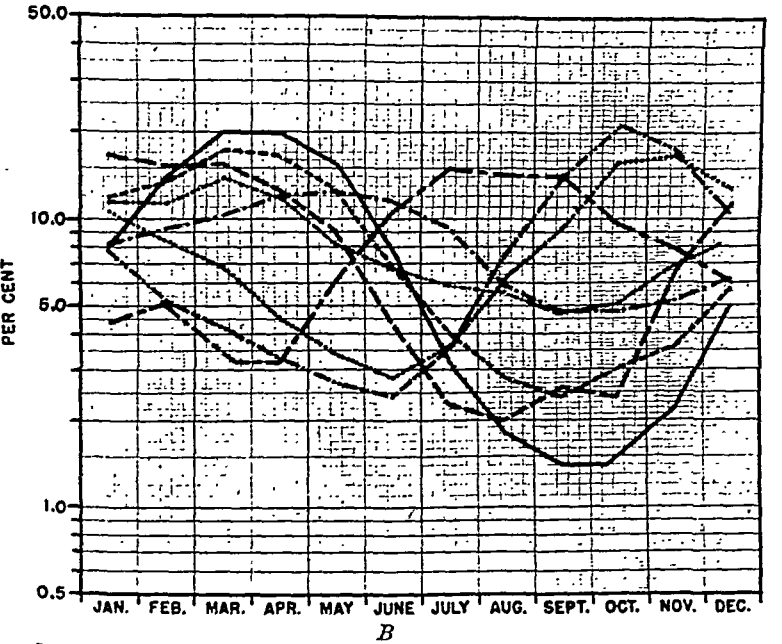
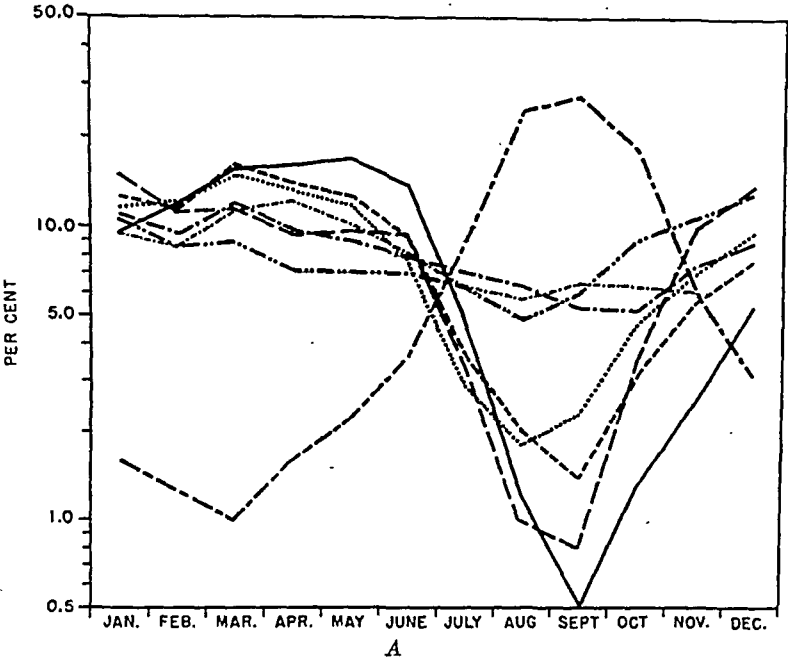
**Crowding.** That the dissemination of infectious agents transmitted directly from man to man is favored by closer aggregation of people need hardly be stated. Both rates and extent of dissemination vary directly with density of population, as shown both by urban and rural differences in incidence and age distribution of disease, in urban-rural differences revealed by carrier studies and by immunity surveys, as, for example, the Schick test in diphtheria or the virus neutralization test in poliomyelitis.<sup>3</sup> The association between population density and dissemination reaches its furthest extreme in remote population groups, not large enough to maintain a continuous sequence of transfer from person to person without exhaustion of susceptibles, and in rare instances of "isolated" individuals. The notable example is the outbreak of measles in the Faroe Islands in 1846 following a 60 year absence of the disease, which was the subject of Panum's classic treatise. In Iceland, measles does not occur continuously as in more intermingling population groups, but occurs in epidemics frequently of great intensity, following its reintroduction from without after varying periods of years of complete freedom from the disease. During the period 1911-1939, measles reappeared in Iceland 5 times following intervals of absence of from 1 to 7 years.<sup>10</sup> The first cases in these outbreaks representing the reintroduction of the disease occurred in February, April, July, August and November, and all reached peaks of prevalence in from 3 to 5 months, coming in June, July and November, and twice in January. Following these major outbreaks and continuous with them were 5 discernible secondary increases in cases which are known to represent the movement of the disease into new areas along the limited lines of communication around the periphery of Iceland. A group of explorers came upon a hermit in an inaccessible part of the Snake River canyon. He told his rather unwelcome visitors that he made only one trip a year to the nearest settlement 40 miles away, but stayed just long enough to weigh out his gold dust and get necessary supplies for he always caught cold when he went there. And then he added, "I'll be sick tomorrow because you've been here."<sup>8</sup>

Thus in differently aggregated population groups, measurable degrees of "crowding" are accompanied by corresponding differences in the dissemination of infectious agents. But it cannot be affirmed, nor is there any measurable indication that in a given population the seasonal variation in disease accompanies any corresponding seasonal variation in "crowding."

**Pandemic Influenza.** Pandemic influenza, a disease in which "spread" is a dominant characteristic, does not exhibit seasonal variation in the manner of many of the upper respiratory infections. Peaks of prevalence, usually far more precipitous than the seasonal undulation seen in other upper respiratory diseases are reached not regularly at the same season, but at any time of the year. The lack of seasonal influence on "spread" is strikingly shown by the simultaneous appearance of epidemics, as, for example, in 1918 in the northern and southern hemisphere.

**Difference in Seasonal Prevalence in Diseases With the Same Mode of Spread.** It would be expected that seasonal curves of individual diseases in a group transmitted in the same manner would be secondarily affected by such factors as differences in infectious period and incubation period, as well as by differences in population immunity. However, the effect of these secondary factors would not appear to be sufficient to explain

the wide divergence observed amongst the seasonal curves of common upper respiratory infections in the same area. For example, the difference



- |                 |                    |
|-----------------|--------------------|
| Measles—        | Scarlet fever..... |
| Whooping cough— | Mumps-----         |
| Diphtheria—     | Meningitis-----    |
| Chickenpox—     | Poliomyelitis----- |

CHART 2.—A, Seasonal prevalence in Massachusetts and Connecticut. B, Seasonal prevalence in Alabama and Mississippi. (Data from registration states, Pub. Health Rep., 1925-1939.)

in time between the peaks of prevalence of diphtheria and meningitis is actually greater than that between diphtheria and certain diseases classified as "occurring in the opposite season" to that of the upper respiratory infections. If any single seasonal factor, like "crowding" were a major influence in the seasonal prevalence of all of the group of upper respiratory infections, it would be difficult to account for such differences in seasonal curves both in northern and southern latitudes as are shown in Charts 2a and 2b.

**Seasonal Virus Harborage.** There now have been established by bacteriologic methods carrier rates which do not vary with season as does the disease which the parasite causes. The prevalence of Type 1 meningococci does not show seasonal differences corresponding to the seasonal variations in the incidence of meningococcus meningitis. The carrier rate for *H. influenzae* remains more or less constant at a high level throughout the year, suggesting that upper respiratory transmission from person to person occurs as readily at one season as another. Although generally considered to be a saprophyte in the adult, these microorganisms occasionally cause meningitis in children, but as with the meningococcus, disease occurs only in a few of those exposed, at a particular season, and is not necessarily associated with any increase in the carrier rate in the population group in which the cases occurred.

The seasonal increase in hemolytic streptococcus carrier rates has been interpreted as a precursor of an outbreak of streptococcal disease.<sup>32</sup> However, it is not yet clearly established that an increase in the number of carriers is the cause rather than the result of disease in a given population group. Carrier studies are not infrequently initiated in populations in which disease is occurring. Thus a "normal" carrier rate may be given undue weight by the fact that the study is done in the presence of disease occurrence. Furthermore, the seasonal fluctuation in hemolytic streptococcus carrier rates is due to fluctuations in the prevalence of Group A strains, the non-Group A strains remaining at a more or less constant level throughout the year.<sup>31</sup> It seems that if "crowding" *per se* were the explanation for seasonal differences in prevalence, then the non-Group A strains should show similar variation—unless one is willing to apply a hypothesized seasonal difference in "transmission" to a particular group of strains. With reference to seasonal differences in the prevalence of carriers, it should be remembered that seasonal variations in host receptivity to the organism could as well be a factor as seasonal differences in "transmission" as the result of crowding.

**Seasonal Variation in Disease Under Uniform Conditions of Infection.** Under experimental conditions where the actual transfer of the infectious agent can be held constant, seasonal variation in the resulting disease still occurs, which in certain instances, corresponds closely to seasonal variations in the natural disease.

Südmersen and Glenny<sup>36</sup> observed a seasonal variation in the toxicity of diphtheria toxin for guinea-pigs. Their observations, when expressed in terms of susceptibility, result in a curve remarkably similar to the curve of the seasonal distribution of diphtheria in the northern United States. Pritchett,<sup>28</sup> working with 5 genetically different strains of mice, observed seasonal fluctuations in susceptibility to paratyphoid-enteritidis infection from a low point in the summer months, increasing through the fall and reaching a peak in early spring. Although there were strain differences in degree, the susceptibility of each strain showed similar seasonal variations. Webster<sup>40b</sup> pointed out that the death rates resulting from a spontaneous outbreak of *B. leptisepticum* infection in a rabbit colony showed a seasonal



variation similar to that observed in experimental mouse typhoid. In view of his previous observation<sup>40a</sup> that in an experimental epidemic the virulence of a given strain remained constant, he suggested that the curve of seasonal fluctuation in mortality in the natural epidemic was due to seasonal variations in host resistance rather than to any microbial change concomitant with the occurrence of the epizootic. Brown and Pearce<sup>4b</sup> have demonstrated a seasonal variation in the susceptibility of rabbits to experimental syphilis, the peak of susceptibility occurring in the late winter and early spring months. Brown, Pearce and Van Allen<sup>5a</sup> reported a similar seasonal fluctuation in susceptibility of rabbits to a transplantable neoplasm. Lillie, Dyer, Armstrong and Pasternack<sup>18</sup> over a period of years, found the intensity of cerebral reaction of mice to St. Louis encephalitis virus, and that of guinea-pigs to endemic typhus rickettsia to be greatest in summer and least in winter. Thus under these experimental conditions where the infectious agent can be held constant in respect to strains, "virulence," dosage and manner of administration, seasonal variations in disease still occur, and these seem clearly ascribable to variations in the test animals. This interpretation finds support in the more basic observation of marked differences in the response of different family lines of experimental animals to the same infection.<sup>19,40c</sup>

**Seasonal Variation in Non-infectious Disease.** A number of non-infectious diseases are subject to seasonal variation to an extent equal to that of infectious diseases. This fact in itself is enough to show that seasonal variations may result from causes other than mode of spread. Seasonal variation in non-infectious disease may result either from variation in environmental factors or from variation in reaction to the impact of a constant environmental factor, as in pellagra. The seasonal character of pellagra was one of the important bases of the theory advanced early in the study of pellagra that it was an infectious disease. The similarity in the character of seasonal curves of infectious diseases and non-infectious disease suggests that a common factor—like seasonal variation in the host—is involved in both, rather than causes as different as rate of spread and dietary habits.

**Seasonal Variation in Physiology.** Despite the accumulated evidence that the physiologic range within which the "normal individual" remains "normal" may be subject to wide variation because of extrinsic as well as intrinsic influences, the possibility that the host may vary with season in respect to its reaction to infection has not yet been generally considered as a possible determinant of seasonal distribution of disease. Perhaps the slowness to readily include host variation in epidemiologic concepts has been due to the lack of proper tools for precise studies of the human host with respect to variable reaction to a given infectious agent—such studies not lending themselves readily to the application of bacteriologic techniques usually employed in the study of infectious disease.

There is, however, considerable experimental evidence from other fields on the effect of season on physiology. Seidell and Fenger<sup>23</sup> have shown that there is a seasonal variation in the iodine content of the thyroid gland of sheep, cattle and hogs, and that different seasonal curves are obtained in different latitudes. Martin<sup>24</sup> reported that the iodine content of thyroids collected from sheep in England showed the same variation, although less than that observed in the northern United States where seasonal changes are greater (Chart 3). During the course of their studies on experimental syphilis, Brown, Pearce and Van Allen<sup>5b</sup> observed a seasonal variation in the organ and gland weights of normal rabbits. Certain of

these variations assumed a seasonal cycle similar to those just mentioned, while almost exactly reversed or reciprocal curves were obtained in the weights of other glands.

Brown and Pearce<sup>46</sup> demonstrated experimentally that seasonal variations in the susceptibility of rabbits to experimental syphilis can be accounted for by variations in the degree of exposure to light. Pearce and Brown<sup>26</sup> showed a similar effect of light on the susceptibility of rabbits to a transplantable neoplasm. The observation by Kligler and Weitzman<sup>17</sup> that increased exposure to light increases the susceptibility of guinea-pigs to trypanosome infection provides an example of the same seasonal factor (light) affecting the animal economy in such a way that opposite effects are brought about on host resistance in two species—increased resistance to *T. pallida* in rabbits and increased susceptibility to trypanosomes in guinea-pigs.

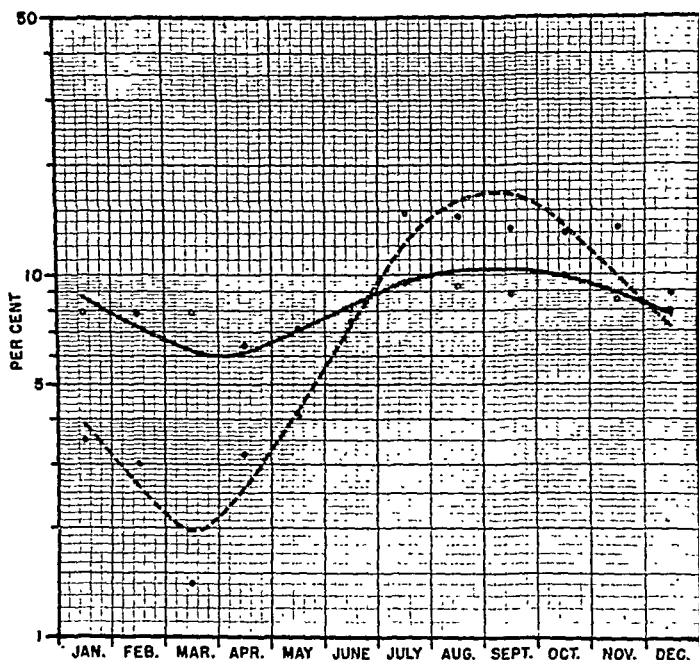


CHART 3.—Seasonal variation in iodine content of thyroid gland in cattle in the United States and sheep in England. Sheep ———; cattle — — —. (Reprinted from J. Prev. Med., 3, 245, 1929.)

Arnold and Brody<sup>1</sup> found that exposure to high temperature and humidity depressed the normal gastro-duodenal bactericidal action in the dog, permitting an increased passage of bacteria from the stomach and duodenum to the cecum. In repeated observations from which it must be concluded that seasonal fluctuations in the efficiency of normal defense mechanisms do occur, Wilson<sup>42</sup> and Pritchett<sup>28</sup> observed similar seasonal fluctuations in the mortalities resulting from experimental mouse typhoid, which under the conditions of the experiment can best be explained by seasonal variation in host resistance. Moragues and Pinkerton<sup>23</sup> reported that mice of the same stock strain showed widely different mortality rates following injection with the rickettsia of typhus fever when kept at different temperatures—the higher temperatures rendering the mice more susceptible. Colvin and Mills<sup>6</sup> pointed out that mice adapted to life in a

moist, high temperature are more susceptible to infection than those adapted to life in cooler environments.

These studies, as well as those of Südmersen and Glenny<sup>36</sup> with diphtheria toxin and of Hunt<sup>14</sup> with acetonitrile, suggest that the physiologic variations brought about by seasonal and environmental changes may be closely related to differences in host receptivity which, in turn, may be one factor determining the seasonal pattern of disease. The significance of these studies lies in the fact that they indicate that the host is not in a state of physiologic stability, but, rather, undergoes seasonal changes of a character similar to the seasonal periodicity of disease. Such variations can hardly be considered as abnormal or pathologic, but as normal adjustments of the host to variations in its environment. As Hunt<sup>14</sup> said, "... man is doubtless daily producing profound effects upon his resistance to poisons and diseases . . . ." The relationship between such physiologic variation and susceptibility to disease perhaps lies in a failure of such adjustment in some respect, resulting in a physiologic imbalance.

That the frequency with which infection results in clinical disease or immunity without disease in the human host may be determined by factors residing entirely within the host seems well established in diphtheria. The Negro race enjoys a comparative freedom from clinical diphtheria despite ample evidence that infection and immunization take place as readily as in the white race.<sup>2a</sup> Studies in familial susceptibility to poliomyelitis,<sup>2b</sup> leprosy,<sup>2d</sup> tuberculosis,<sup>2g</sup> diabetes<sup>2h,16</sup> and rheumatic fever<sup>43</sup> have indicated that the major determinant of disease often is within the host. Experimentally, the studies of Webster<sup>40c</sup> on mice and of Lurie<sup>19</sup> on rabbits have clearly established that susceptibility to a given infectious agent may be determined by host factors. Indeed, in experimental bacteriology, the selection of the proper strain of experimental animal has become a laboratory commonplace.

The observation that clinical disease results in but few of the many exposed to the same infectious agent is good indication that the receptivity of the host is determined in part at least by factors other than acquired or induced immunity. Paralytic poliomyelitis occurs in few of those infected with the virus—indeed clinical disease, either paralytic or non-paralytic, is relatively infrequent when it is remembered that exposure to the virus is almost universal. The incidence of bulbar poliomyelitis following tonsillectomy provides a good example of an induced autarceologic change precipitating disease in a virus carrier.<sup>24</sup> The pneumococcus carrier, too, has been observed to suddenly develop pneumonia for reasons not yet clearly defined, due to the same type of organism he has harbored for some time.

Susceptibility, as measured by the Dick test, is generally taken to indicate susceptibility to scarlet fever. However, it has been repeatedly shown among school children attending the same grade in the same school that a Dick positive may harbor the identical strain of hemolytic streptococcus producing scarlet fever in the child at the next desk, and will develop either a mild "sore throat" or no clinical illness at all; the Dick test in such case often remaining positive.<sup>37</sup> Furthermore, a known toxigenic strain may attain the same degree of dispersion in two groups of similar age and immunity status, and will produce disease in one group while remaining innocuous in the other group.<sup>9</sup> Such observations suggest the existence of factors other than susceptibility to erythrogenic toxin which determine in part whether or not clinical infection follows exposure. Rheumatic fever, a serious sequel to streptococcal infection, is precipi-

tated in relatively few of the many infected at some time or other with the hemolytic streptococcus. The same is true of meningococcus meningitis. A comparison of the carrier rate for Type 1 meningococcus with the incidence of clinical disease makes it clear that a very small percentage of those who harbor the organism develop meningitis.

There is some evidence that differences in host resistance are determined by physiologic as well as genetic differences. Among these physiologic variations, differences in the economy of the endocrine hormones may be one factor which influences the reaction of the host to a given infectious agent.<sup>2b</sup> As is well known, pregnancy affects the development or progress of several diseases. These effects may be the net result of mechanical or nutritional stress, or may be the result of some intrinsic physiologic factor associated with the utilization of the sex hormones. Pregnancy may be a predisposing factor in lethargic encephalitis<sup>20</sup> and poliomyelitis.<sup>2f</sup> On the other hand, there is no adequate explanation for some of the effects noted—the “therapeutic” effect of pregnancy on syphilis,<sup>35</sup> or the resistance of pregnant and lactating animals to experimental syphilitic infection.<sup>4a</sup> Experimental studies indicate that the estrogenic substances exert a protective effect against the intranasal instillation of poliomyelitis virus in monkeys,<sup>2d</sup> and against pneumococcal<sup>39a</sup> and streptococcal<sup>7</sup> infection in mice, while the opposite—an enhancement of the disease process—has been observed in experimental tuberculosis in guinea-pigs.<sup>37</sup>

There is evidence of significant changes in the condition of the nasopharynx, a common portal of entry for infection, brought about by changes in temperature and humidity, which may well be related to host resistance. Hill and Muecke<sup>12</sup> showed that the nasal mucosa remains swollen and edematous for some time following exposure to a warm, moist atmosphere. Mudd *et al.*<sup>25</sup> found that body chilling is associated with a marked drop in the temperature of the nasal and postnasal cavities.

As long ago as 1896, Malling-Hansen<sup>22</sup> observed seasonal variations in weight increase in children—the greatest weight increase occurring from August to the middle of September, and the least during early spring and summer. Vahl<sup>38</sup> found that female children gained weight faster in summer than winter, while Porter<sup>27</sup> observed that the weight gained by male children in the first and last 5 months of the year was in the ratio of 1 to 4.1.

Aycock<sup>2a</sup> found that in Massachusetts the average number of cases of poliomyelitis occurring in the first 5 months of the year was 1 to 4.2 to those occurring during the last 5 months of the year. In Chart 4 the average percentage gain in weight each month (Porter's study) is compared with the seasonal distribution of poliomyelitis.

That seasonal physiologic differences do exert a definite influence on the seasonal prevalence of disease is emphasized by the fact that susceptibility to certain non-infectious diseases (where the factors of “seasonal transmission” and “microbic variation” need not be considered) exhibit characteristic seasonal variations, *e. g.*, pellagra. Rickets furnishes another example of the influence of physiologic variation on seasonal fluctuation. Hess and Lundagen<sup>11a</sup> found a seasonal variation in the blood phosphate of infants which corresponds closely with the seasonal variation of healing rickets, as described by Schmorl.<sup>30</sup>

**Reciprocal Seasonal Prevalence.** In general, seasonal curves which are different in shape even though they may reach their peaks at the same season are suggestive of the operation of different and unrelated mechan-

isms. Where 2 diseases have seasonal curves which are either identical with or exactly the reverse of each other, the operation of the same influence on the 2 diseases, either in the same or in the opposite manner is suggested.

As already pointed out, the season of prevalence of epidemic typhus fever (European) is the reverse of that of other insect-borne diseases as a group. Furthermore, the shape of the seasonal curve of louse-borne typhus is not only different but almost the exact reciprocal of that of flea-borne American typhus (Chart 5). Ample evidence affords the explanation, of course, that the two forms of the disease have reversed seasonal curves, not because of different and unrelated mechanisms of spread, but because the 2 insect vectors thrive under opposite seasonal influences.

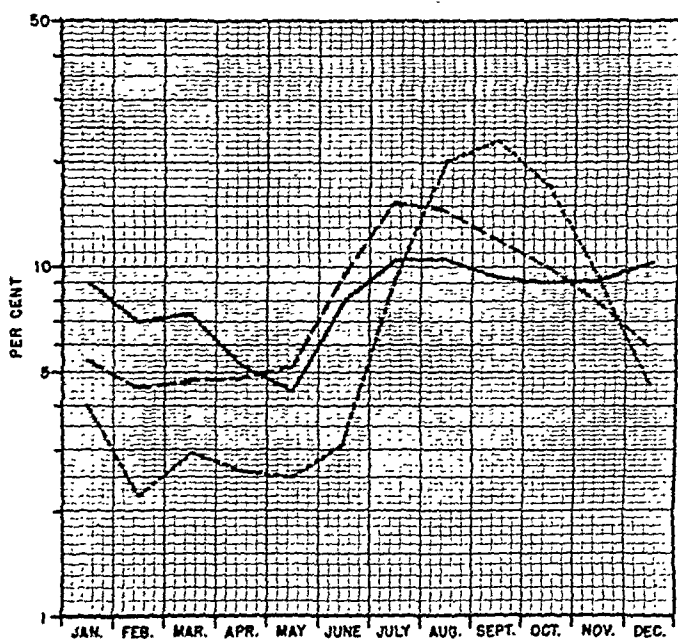


CHART 4.—Seasonal variation in average percentile gain in weight in school children as compared with seasonal fluctuation in poliomyelitis. Poliomyelitis: Massachusetts -----; Southern ———. Rate of growth ———. (Reprinted from *J. Prev. Med.*, 3, 245, 1929.)

Thus, typhus fever furnishes an example of the same principle of transmission producing reversed seasonal curves due to opposite effects of the same influence (season) on 2 different vectors—the 1 being favored in the same order as the other is inhibited by season.

A classical experimental example of reciprocal seasonal effects of the same mechanism is seen in the work of Reid Hunt<sup>14</sup> many years ago, wherein it was shown that the seasonal curves of toxicity of acetonitrile for mice and for guinea-pigs were almost exactly the opposite (Chart 5).

Most of the ordinary poisons undergo no marked chemical changes in the body before exerting their toxic effects. Acetonitrile, however, is poisonous only, or largely as a result of the formation from it of hydrocyanic acid, according to Hunt. The formation of hydrocyanic acid is due to certain processes of metabolism which are seasonal and may be modified by factors which influence metabolism as, for example, diet or

the administration of thyroid. Numerous experiments showed that minute amounts of thyroid fed to rats and guinea-pigs increased susceptibility of these animals to acetonitrile. The opposite effect—increased resistance to this poison, is produced when thyroid is fed to mice.

Hunt suggests as an explanation of this seemingly paradoxical reaction that in mice acetonitrile tends to be changed to acetamid and that in mice thyroid increases this reaction rather than the formation of hydrocyanic acid, the reaction which is increased by the administration of thyroid to rats or guinea-pigs. Hunt's suggestion is based on the fact that acetamid has the same odor as that which is peculiar to mice, although it has never been shown that the characteristic odor of mice is actually due to the presence of this substance.

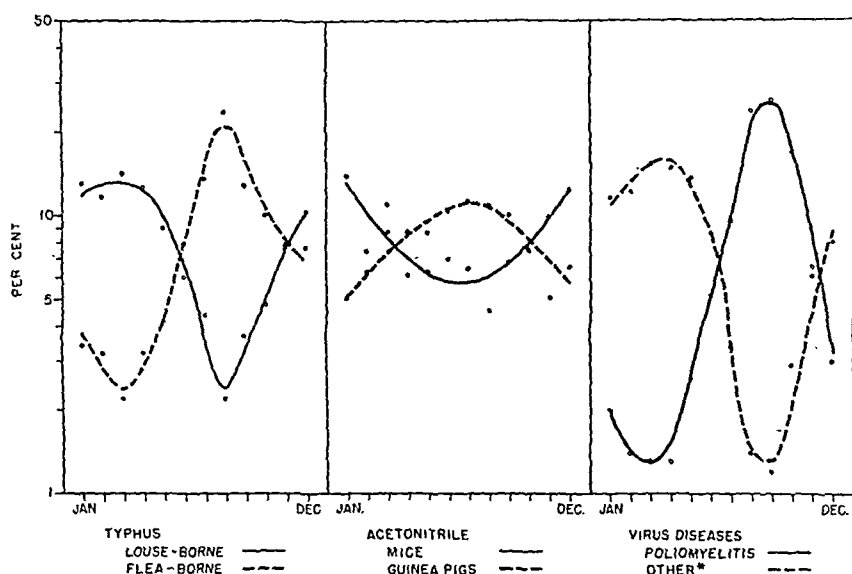


CHART 5.—Reciprocal seasonal curves, in the same virus disease, in the toxicity of the same poison, and in virus diseases in the same host, as determined by reversed activity of different vectors, different hosts, and different virus. (Data from League of Nations Bull., 1929-1934; Hyg. Lab. Bull., No. 33, 1907; No. 69, 1910.)

Thus the acetonitrile phenomenon affords an example of the opposite seasonal effect of the same toxic agent—administered in the same way in 2 animals. Here the reciprocal seasonal effect is clearly due to the fact that the 2 different experimental animals possess different faculties of metabolizing the acetonitrile—the one in the direction of toxicity and the other in the opposite direction. Since seasonal variation in metabolic processes are the same in the 2 animals, the result is a reversal of seasonal curves of toxicity in the 2 experimental animals.

If the acetonitrile be likened to virus and its administration to mode of spread, the acetonitrile phenomenon becomes a good analogy in the epidemiologic sense to the same virus transmitted in the same way producing reciprocal curves of seasonal prevalence in 2 different hosts. And it may be commented here that if the seasonal curves in the 2 animals were the only data presented, it would hardly be inferred by the process of reasoning ordinarily used in epidemiology in interpreting seasonal prevalence, that the 2 animals had been "infected with" the same "causative agent" in the same way.

The modes of spread of practically all infectious diseases are no longer in question. In some, a single basic observation or experiment has been sufficient to settle any question of mode of spread. In others, the mode of spread is clearly indicated by the general features of distribution of the disease. In still others, modes of spread are readily accepted not so much because of anything which can be called proof in the usual sense of the word, but because of similarities in distribution to other diseases in which "proof" has been elicited in one way or another. As already pointed out, seasonal prevalence has been a favorite basis for inference as to modes of spread, and to many, the character of its curve has been enough to stamp a disease as having a given mode of spread.

Poliomyelitis is unique amongst the infectious diseases in that its mode of spread has remained a subject of heated controversy. The classic studies of Caverly, Wickman, Frost, Flexner and Lewis and many others all afford evidence of transmission by ordinary human contact. The evidence in favor of this concept of the epidemiology of poliomyelitis is easily of the order of that readily accepted as conclusive proof in many other diseases. And yet it has been subjected to innumerable checks and challenges. The basis of these objections has always lain in the well-known and constantly reiterated fact that the seasonal prevalence of poliomyelitis is the opposite of that of the contact diseases as a group. A number of studies have grown out of this single objection, the results of which are, to be sure, consistent in themselves with other modes of spread. These have been stressed as indicating other modes of spread, in spite of the fact that similar objections to accepted modes of spread in other diseases can be equally well supported.

A similar challenge to accepted modes of spread in many other infectious diseases doubtless would elicit findings equally inconsistent in themselves with accepted modes of spread. Poliomyelitis not only reaches its peak of prevalence in the opposite season from that of a number of the upper respiratory infections, but, as in the 2 examples cited, typhus fever and acetonitrile, its seasonal curve is the reciprocal of that of the composite seasonal curve of a number of upper respiratory virus infections (Chart 5). The fact that the seasonal curve of poliomyelitis is the exact reciprocal of that of the upper respiratory group, not merely "reaching its peak in the opposite season," is enough to suggest that it is not due to the operation of a different and unrelated mode of spread, but to the operation in reversed order of the same mechanism which determines the seasonal curve of the group of upper respiratory diseases in general.

It might also be remarked here that the fact that there is a seasonal curve which is the reciprocal of that of the winter upper respiratory group of virus infections might be taken in itself as an indication that the winter-prevalent virus infections are not the direct result of crowding. If it were, its reciprocal curve would suggest the effect of the opposite of crowding—population dispersal—and one cannot conceive of dispersal of population in itself favoring any mode of spread.

Thus in typhus fever, louse-borne or epidemic and flea-borne or endemic; in the acetonitrile phenomenon, in mice and rats or guinea-pigs; and in the seasonal phenomenon of poliomyelitis and the group of upper respiratory virus infections, there are 3 examples of reciprocal seasonal prevalence. In typhus it is clear that the reversed seasonal curves are due not to different mechanisms of spread but, rather, to reversed bio-nomics of the 2 insect vectors. In the acetonitrile phenomenon it is likewise clear that reversed seasonal curves are due to reversed effects of the

same seasonal factor on the conversion of the non-toxic acetonitrile into a toxic substance in the 2 host animals.

In view of the weight of evidence to the effect that the virus of poliomyelitis is transmitted by person-to-person contact, the proposition is made that its seasonal curve is similarly due to the operation in the reversed order of the same factor which is responsible for the seasonal fluctuation in upper respiratory virus infections as a group.

These 3 examples of reversed seasonal prevalence in what can be termed the same mechanism of spread, serve to illustrate the complex nature of parasite—environment—host relationships in epidemiology as well as to emphasize the fact that seasonal prevalence is not a criterion for mode of spread alone, but may reflect seasonal variation in parasites themselves, in environmental factors affecting their transmission, or in the susceptibility or reaction of the host to the disease agent.

**Summary.** "Si nous reprenons maintenant l'examen du problème que soulève la régularité si grande de la plupart de nos maladies épidémiques, une question se pose tout d'abord; ce phénomène est-il du au microbe ou à l'individu atteint?"<sup>21</sup>

A hypothesis early advanced and now become a legend as the preferred explanation of the genesis of epidemics is "increase in virulence of the infective agent by rapid passage." Since in most infections transmitted directly from human to human, "epidemics" are in reality seasonal increases in prevalence, this explanation becomes at the same time the commonly accepted explanation for seasonal prevalence.

The sole basis for the idea of increased virulence as the responsible factor in epidemics is the stepping up in virulence with rapid passage when an infectious agent is first transferred to an experimental animal. There is actually no evidence that this is a reflection of what happens in the natural host, or that increase in virulence in the experimental animal constitutes an increase in virulence for the natural host. On the contrary, there are many indications that it represents a process of adaptation of the organism to an unaccustomed host.

Reasons have been given which indicate that seasonal prevalence in the upper respiratory diseases is not simple seasonal variation in opportunities of transmission of the infectious agents according to the older generalization, but, rather, a far more complex seasonal variation in the parasite—host interaction.

There is no clear-cut evidence that parasites themselves undergo seasonal changes in virulence. Although the *frequency* of disease varies greatly with season, in some cases in the face of uniform prevalence of the infective agent, there is no corresponding variation either in the severity of clinical manifestations or in case fatality rate, as might be expected if the infective agent were undergoing seasonal changes in its pathogenicity. In other words, the character of the disease produced is the same whether it is occurring rapidly and in large numbers, or slowly and in small numbers.

On the other hand, we see many seasonal variations in physiologic activity which are in general considered as normal changes which take place concomitantly with seasonal changes in the environment in which we live. None the less many of these seasonal undulations are of the same character of seasonal fluctuations in disease—non-infectious and infectious. Furthermore, examples have been given particularly in the experimental field where certain of these normal seasonal variations in physiology can be associated with variations in resistance to fixed toxic agents. It is not meant to imply here that seasonal variations in physiology are in them-



selves pathologic. They undoubtedly are normal, adaptive adjustments to the changing environment. It would rather appear that any association with susceptibility to infection resides in faults or failures in seasonal changes in physiology.

As judged from the magnitude of seasonal variations in infectious disease, in harborage of certain infectious agents and in physiologic functions, it is anticipated that the host-parasite interaction may be affected by season in 2 distinct ways. Seasonal changes in the host may have the simple effect of producing a seasonal variation in resistance to disease while not necessarily affecting the harborage or transmission of the infectious agent. On the other hand, both resistance to disease and resistance to infection (multiplication of the virus which in turn affects transmission) may be influenced by season.

Differences in the magnitude of seasonal variation in a number of infectious diseases affords some indication that the former may be a general rule in bacterial infections, and the latter in virus infections—a point, however, which will require further investigation.

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## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 16, 1945

**Hematological Changes Produced by Large Doses of Atabrine.** CHARLES W. MUSHETT and HENRY SIEGEL (Merck Institute for Therapeutic Research, Rahway, N. J.). The oral administration of large doses of atabrine to rats, mice, rabbits, hamsters, guinea-pigs, dogs, monkeys, chickens and ducks resulted in definite hematologic changes. These consisted of anemia, leukocytosis, the appearance of peculiar basophilic inclusions in the cytoplasm of lymphocytes and in erythrocytes and alterations in the differential count. The appearance of lymphocytic inclusions after atabrine therapy was a constant feature in all species, while the other changes varied with the species. With Romanowsky stains, such as Wright's solution, the lymphocytic inclusions appeared as dark blue staining bodies in the cytoplasm varying in size and shape from minute punctate granules to large irregularly shaped masses. These bodies were so large they often caused bulging of the lymphocytes and were frequently associated with increased vacuolization. Inclusions of a similar nature, but smaller in size were irregularly distributed in erythrocytes, particularly in cells with a polychromatophilic staining reaction. While lymphocytic inclusions were seen in all 9 species used, erythrocytic inclusions were observed only in rats, mice and hamsters. Anemia was observed in the rat, monkey and dog. Leukocytosis was noted in the rat and leukopenia in the rabbit, dog and monkey. The differential change usually consisted of a lymphopenia and polynucleosis, while the rat showed, in addition, a monocytosis. It is considered unlikely that the blood changes might be due to the activation of a latent infection, such as that caused by Bartonella or a related organism. It must be emphasized that the dose of atabrine which produces blood changes in laboratory animals is considerably larger than that ordinarily used for the treatment of malaria in humans.

**Reduced Acute Toxicity of Antigens in Saline-in-Oil Emulsion.** SEYMOUR P. HALBERT, JOSEPH SMOLENS and STUART MUDD (Department of Bacteriology, University of Pennsylvania). The degree of reduction of the acute toxicity of various antigens in a saline-in-mineral-oil emulsion has been investigated. The lethal toxicities for mice by the subcutaneous route of the antigens diluted in saline were compared with those of the same antigens prepared as saline-in-mineral-oil emulsions. In most cases, 50% survival doses were determined. The quantitative estimations of the fold decreases of the materials studied are: *S. paradysenteriae* Flexner

V368 antigen, 9 fold; Shiga neurotoxin, 20 fold; Botulinus toxin, 43 fold; Ricin (a plant toxin), 49 fold; tetanus toxin, 100 fold, 326 fold (two experiments).

Other reports have indicated that the oil-emulsion technique improves antigenicity. The above results would seem to indicate that this menstruum offers promise for the reduction of acute toxicity as well.

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**The Behavior of Inhaled Particles in Different States of Aerosol Suspension as Indicated by Pulmonary Tuberculosis in Rabbits.** W. F. WELLS and H. L. RATCLIFFE (Laboratories for the Study of Air-borne Infection and Department of Pathology, School of Medicine, University of Pennsylvania). Settling velocity is probably the most important physical characteristic of air-borne particles. It integrates the elementary features of size, density and shape, upon which depend the pollution and purification of air. Since air drag, weighed by settling velocity, carries particulate matter into the respiratory tract, particles of different settling velocity are likely to result in different disease patterns from air-borne infection.

Several years ago, an apparatus for the simultaneous exposure of rabbits up to the number of 6 to inhalation of quantitative doses of air-borne infection was exhibited to the Society. Last year procedures for the suspension of particles of uniform size and the determination of their settling velocity were described. Wells and Lurie had previously shown that tubercle bacilli in nuclei settling less than one-tenth of a foot per minute were almost quantitatively inhaled into the lung of rabbits, and in 4 weeks these developed into discrete tubercles which could be readily counted. The tubercle bacillus therefore appears to be a suitable tracer organism for the quantitative determination of the deposition of inhaled particles in the alveoli.

Experiments have since been conducted using improved apparatus and techniques by which particles of uniform settling velocity may be inhaled. The number of tubercles produced by inhalation of particles settling a foot a minute has been compared with the number produced by approximately the same number of infected nuclei settling less than a tenth of a foot a minute. In these experiments broth cultures of the Ravenel strain were grown in revolving Erlenmeyer flasks with beads. The process breaks up the growing mass of organisms, so a filtrate through a No. 4 Whatman filter shows a majority of the organisms to be in single form which can be counted by the Breed method. Equal quantities of this suspension were added to a 1% and a 40% solution of Difco brain-heart medium and atomized into the air which the rabbits breathed for 30 minutes.

In 1 experiment 4 rabbits exposed to the small nuclei settling less than a tenth of a foot a minute gave, after 4 weeks, 1 negative, 2 with single tubercles in the lung, and 1 with 2 tubercles in the lung. Four rabbits exposed to nuclei settling a foot per minute showed no tubercles after 7 weeks. In a second experiment using larger numbers in the aerosol, 5 rabbits breathing the smaller nuclei gave 22, 16, 21, 26 and 17 tubercles at the end of 4 weeks. Four rabbits breathing the larger nuclei gave 4, 3, 3 and 5 tubercles in the lung. In a third experiment 6 rabbits inhaling somewhat larger nuclei showed 5, 6, 4, 13, 20 and 15 tubercles at the end of 30 days. All 5 similar rabbits breathing the smaller nuclei showed more than 100 tubercles each in the same time. No evidence of infection of other organs in the body was found. The fate of the organisms which did not reach the lung has not yet been ascertained.

In view of the fact that nuclei from body fluids coughed or sneezed into the atmosphere may be of the dimensions of the smaller nuclei, while particles of dust raised from dried sputum would probably be coarser than the large nuclei, these experiments would seem to be significant in a study of air-borne infection. Most of the bacteria-bearing particles observed in normal inhabited atmospheres are of the order of magnitude of the larger nuclei and the coarser fragments from infected clothing or bedding would probably be even greater. There may be a difference in the mode of infection of the nose and throat, by organisms such as streptococci or diphtheria bacilli in infected dust and the so-called contagious virus infections which spread dynamically through aggregations sharing confined atmospheres.

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**Osmotic and Ionic Equilibria Between the Erythrocyte and a Complex External Solution.** M. H. JACOBS and DOROTHY R. STEWART (Department of Physiology, University of Pennsylvania). The nature of the osmotic and ionic equilibria between a normal erythrocyte, permeable to all anions and no cations, and its normal surrounding medium, the plasma, has been discussed in detail by Van Slyke, Wu, and McLean. In experimental work with drugs which are weak bases it is necessary in addition to consider penetrating molecules and what in effect are penetrating cations. Other situations may arise which involve non-penetrating anions and non-electrolytes. All possible cases of this sort, numbering several hundred, may be dealt with together by considering the most complex case possible, namely, that in which penetrating and non-penetrating anions, cations, and molecules, respectively, and proteins are all present in the external medium. The problem involves the determination of 6 unknowns, *i. e.*, the internal pH of the cell, the degree of ionization of its hemoglobin, its water content and the distribution ratios for penetrating anions, cations and molecules, respectively. To find these 6 unknowns, 6 relations among them are available, which, when properly combined, lead to a relatively simple solution. Appropriate equations for the simpler particular cases that arise in practice are obtained by substituting in the general solution the value zero for all the missing quantities. Four such equations when applied to the distribution of salts of weak bases explain in part the low distribution ratios reported for such substances in the case of the erythrocyte, the inapplicability of Nernst's distribution law, the swelling of the erythrocyte in the presence of ammonium salts, and other observed facts. An application of these principles gives a method for the detection of ammonium salts in concentrations at least as low as 0.00003 M.

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**Changes in the Non-protein Fractions of the Plasma Nitrogen Following Extensive Thermal Burns.\*** JAMES WALKER, JR. (Pennsylvania Hospital and Harrison Dept. of Surgical Research, Univ. of Penna.). In a study of the toxemia syndrome in over 100 thermal burns, detailed analyses of the non-protein nitrogen fractions of the plasma nitrogen were carried out in 18 patients. It was observed that the severity of the clinical picture seemed to be closely correlated with the elevation of the plasma non-protein nitrogen and that all of the patients in the larger series in whom the non-protein nitrogen rose to above 100 mg. per 100 ml. of plasma died. Urea nitrogen, uric acid nitrogen, creatinine nitrogen and alpha amino nitrogen were analyzed separately and seldom increased very much.

\* Work done under contract with the Office of Scientific Research and Development.

Fifty to 80 % of the rise occurred in the undetermined fraction of the non-protein nitrogen. The level of this undetermined fraction rose rapidly and progressively in most of the fatal cases. In non-fatal cases in which the clinical picture of toxemia developed it rose for a time and then fell irregularly.

In fatal cases there was autopsy evidence of severe injury to the kidney tubules but in spite of this, nitrogen output was gradually increased in the urine and fractionation of urinary non-protein nitrogen revealed that 30 to 50 % of the increase was in the undetermined fraction.

Whether any of this undetermined nitrogen represents a toxic factor or whether it is merely a response to tissue injury remains uncertain.

# BOOK REVIEWS AND NOTICES

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A TEXTBOOK OF PATHOLOGY. Pathologic Anatomy in Its Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease. By ROBERT ALLAN MOORE, Edward Mallinckrodt Professor of Pathology, Washington University School of Medicine, St. Louis. Pp. 1338; 513 figs.; 34 in color. Philadelphia and London: W. B. Saunders, 1944. Price, \$10.00.

THIS new textbook replaces in the Saunders' list that classic, McCallum's Textbook of Pathology, which recently has been discontinued with the death of Dr. McCallum. This is obviously a tough assignment. Despite this psychologic handicap, the book gets off to a good start and will undoubtedly be a strong competitor in its field.

The organization of the book is unusual, being a compromise between the conventional pattern of general, followed by systemic, or special, pathology and the modern attempt to arrange on an etiologic basis. The major division into general and special pathology is conventional, with sections arranged from various points of view.

In the general pathology section, degenerations are divided into disturbances of protein, carbohydrate, lipid, and mineral metabolism, rather than the more usual descriptive anatomic approach. On the whole this is a distinct improvement. However, it does have the disadvantage of implying more precise knowledge of many of these obscure processes than is accepted by most pathologists. A separate chapter on the disturbances of body fluids is a welcome innovation in pathology texts.

Following the general pathology section is a group of chapters dealing with various types of infections. These have been classified on the basis of the portal of entry. Thus, chapters are given over to such portals as the skin, respiratory, alimentary, and genital tracts. This classification leaves a large group of miscellaneous infections, other bacteria, rickettsia, viruses, fungi, and parasites, to be taken up in separate chapters.

Major subdivisions are then given to diseases caused by physical agents, chemicals, pregnancy and the newborn, and deficiencies.

The last half of the book is a review of diseases of unknown cause. Those of each system and organ are taken up in separate chapters, in the conventional systemic method of special pathology.

The text "reads" easily and is well documented, especially as regards summarizing articles. The illustrations are excellent, a high percentage being actual photographs, many in color, with many good drawings from McCallum's book. The book is well printed on excellent paper, exceptional in these war days.

All agree that an "etiologic classification" of disease is a desirable ideal. When infectious diseases are to be discussed such a method is a necessity. However, in a textbook of pathology such a small part of the lesions discussed fall readily into this group that it seems doubtful whether the orderly systemic classification should be upset more than is necessary in order that this special group may receive the best treatment. It is the Reviewer's opinion that none of the new classifications, either Dr. Moore's or those of other standard texts, have any advantage over the old conventional systemic classification.

Dr. Moore has made full use of the "etiologic classification." This makes for excellent organization in some portions, but is clumsy and inconvenient when the same organism, streptococcus, let us say, produces important lesions with different disease pictures in various parts of the body. Other innovations seem of doubtful value, especially that of classifying diseases by portal of entry. Also when considering diseases of an organ, it is disconcerting and often

inconvenient to have to look in many widely separated chapters for the various types of lesions. It seems to the Reviewer that the resulting incoördination is too high a price to pay for the partial attainment of an "etiological classification."

On the whole, however, Dr. Moore has done an excellent job. As a student textbook, this book should undoubtedly take its place as an equal with other standard works. Pathologists will find it of value for quick reference and its bibliographies of value for locating summary articles. It can be recommended for both student and specialist.

W. S.

**ENDOCRINOLOGY OF WOMAN.** By E. C. HAMBLÉN, B.S., M.D., F.A.C.S., Clinical Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Chief of the Endocrine Division and Endocrinologist, Duke Hospital, Durham, N. C. Pp. 571; 157 figs. Springfield, Ill.: Charles C Thomas, 1945. Price, \$8.00.

THE first half of the book deals with the anatomy and the normal and applied physiology of all the endocrine organs, and diagnostic methods. The second half treats of endocrine diseases, with special emphasis on gynecologic conditions. The text is designed for practical clinical usefulness, and it is systematically and concisely written. Although there are two chapters on the thyroid, no mention is made of non-toxic nodular goiter. Numerous illustrations are from the author's material and reproductions of charts and tables from publications by others. Many references are given at the bottom of the pages and at the end of the chapters.

The Reviewer protests, on the grounds of moral principles, against the author's advocating masturbation to obtain seminal fluid. The author's opposition to the use of androgens in women is to be commended. The Reviewer dislikes the author's insistence that the mother shall not be present during the vaginal examination of her child, and deplors a number of other expressions of his point of view.

I. Z.

**MEDICAL USES OF SOAP.** Edited by MORRIS FISHBEIN, M.D. With 10 Authors. Pp. 182; 41 figs. Philadelphia: J. B. Lippincott, 1945. Price, \$3.00.

ALTHOUGH scattered articles, a number by some of the present authors, have appeared in the literature on soap, this book represents a complete symposium on the medical uses of soap. Between two covers one can obtain authoritative answers to the questions usually asked by patient and physician alike about soap, detergents, and similar subjects.

This book should rightfully be called *Soap, a Medical Problem*.

The range of material includes: (1) Soap Technology; this is a discussion of the chemistry and manufacture of soap, a presentation of the new detergents, and the mechanism of detergency or cleansing action. (Daniel J. Kooyman and G. Thomas Halberstadt.) (2) Usual or Normal Effects of Soap on the "Normal" Skin. (3) Unusual or Abnormal Effects of Soap on the "Normal" Skin. (4) The Effects of Soap on the Abnormal or Diseased Skin. (Marion B. Sulzberger and Rudolf L. Baer.) (5) The Effects of Soap on the Hair. (Theodore Cornbleet.) (6) Soaps for Industry and the Industrial Worker. (Carey McCord.) (7) Soap for Shaving. (Lester Hollander.) (8) Cutaneous Detergents Other than Soap. (C. Guy Lane and Irvin H. Blank.) (9) The Medical Uses of Soap. (Morris Fishbein.)

A fine production, this book is worthy of the consideration of all physicians especially general practitioners, industrial physicians, and dermatologists. It is a good reference book for anyone, medical or lay, who is interested in soap.

H. B.

**METASTASES.** Medical and Surgical. By MALFORD W. THEWLIS, M.D., Attending Specialist in General Medicine, U.S.P.H. Hospitals, New York City; Attending Physician, South County Hospital, Wakefield, R. I.; Special Consultant, Rhode Island Dept. Public Health; Author, *Care of the Aged (Geriatrics)*, Preclinical Medicine. Foreword by HUBERT A. ROYSTER, A.B., M.D., F.A.C.S., Honorary Chief Surgical Service, Rex Hospital; Chief-of-Staff, St. Agnes Hospital; Consulting Surgeon, Dix Hill State Hospital; Fellow, American Board of Surgery, Raleigh. Pp. 230; 13 ills. Charlotte, N. C.: Charlotte Medical Press, 1944. Price, \$5.00.

It is unbelievable that this volume could be offered in good faith as "helpful to students, to general practitioners, to busy surgeons or to roentgenologists who want to refresh their memories." From Foreword to finish this book represents the most ridiculous jumble of nonsense and errors that the Reviewer has encountered in modern medical literature. An excerpt from the Foreword states that "Even if the 'cause of metastasis is not known' ready recognition of its possibilities will save lives. Study of this volume will contribute effectively to that result." The author's Preface informs us that "This book is an outline of medical and surgical metastases, merely an adjunct to three-dimensional anatomy and pathology." The scope and arrangement of the volume is described by the author as follows: "General considerations are given in Section I; in Section II neoplasms are *considered*; in Section III infections are *recorded*; in Section IV infectious diseases are *noted*; in Section V miscellaneous diseases are *taken up*; and in Section VI regional areas are *discussed*." [Editor's italics.]

"The following references in the text are given: A, type or site of primary lesion; B, source of metastases; C, location of metastases."

The section on General Considerations commences with the following illuminating discussion of the term metastasis: "Metastasis is defined as 'the transfer of a disease process from a primary focus to a distant one by the conveyance of the causal agents through blood vessels or lymph vessels.' The term metastasis may be applied to 'movement of bacteria from one part of the body to another; or a change in location of a disease or of its manifestations or transfer from one organ to another.' It also applies to the 'subsidence of an inflammation that at the same time appears in another part' (Taber). The prefix meta is used to denote change of place, order, condition or nature; stasis is stagnation or stoppage of the circulation of any fluids of the body."

The text of Sections II to VI consists of list of primary sites and locations of metastases. For example (pp. 33-34): "Adamantinoma: A. Hypophysis; Jaw, especially lower jaw; Lung; Lymph-nodes; Nasopharynx; Orbit; Pituitary gland; Tibia. [No B—Ed.] C. Rarely metastasizes. Slow growth. To: Glands, cervical; Lung; Ovary; Tibia." [The author's tabular arrangement of this and the following quotation has been altered to save space.—Ed.] Why hypophysis and pituitary gland are listed separately is not clear. It is also rather disconcerting to learn that adamantinomas arise in so many localities. Also perplexing is to discover that bronchogenic cancer metastasizes to osteoarthropathy (p. 37) and that fibrocarcoma (presumably fibrosarcoma) does not often metastasize (p. 40). One more example taken from the section on neoplasms (pp. 51-52) will suffice): "Schuller-Christian Syndrome (Exanthematosis): A. Bone; Skin, especially of eyelids. C. To: Ascites; Bone (defects in skull and long bones); Brain; Diabetes insipidus; Exophthalmos; Joints; Liver; Lungs; Lymphnodes (regional); Lymph nodes; Perinephric suppuration; Perinephritis without suppuration; Peritoneum; Pleura; Ribs; Spleen."

Enough? Or must I include sickle-cell anemia metastasizing to fat embolism (p. 83) and biliary cirrhosis metastasizing to osteoarthropathy (p. 85) to convince the reader of this review that he had better spend his \$5.00 on War stamps? One wonders whether the author and his publisher are aware of the paper shortage in this country.

D. C.



**ADVANCES IN PROTEIN CHEMISTRY. VOLUME I.** Edited by M. L. ANSON, Continental Foods, Hoboken; JOHN T. EDSALL, Harvard Medical School; and 9 Contributors. Vol. 1. Pp. 341; numerous figs. and tables. New York: Academic Press, Inc., 1944. Price, \$5.50.

This is the first volume of a projected series dealing with advances in various fields of protein chemistry. Eight contributors discuss proteins as they occur in complex biologic systems of nature—fields that have been neglected in many of the recent monographs on proteins.

The range of topics discussed is indicated by the titles of the chapters: Lipoproteins (E. Chargaff), Structural Proteins of Cells and Tissues (F. O. Schmitt), Some Contributions of Immunology to the Study of Proteins (H. P. Treffers), The Interaction Between Alkali Earth Cations, Particularly Calcium, and Proteins (D. M. Greenberg), The Purification and Properties of Certain Protein Hormones (B. F. Chow), Soybean Protein in Human Nutrition (D. S. Payne and L. S. Stuart), Nucleoproteins (J. P. Greenstein), and The Proteins of Skeletal Muscle (K. Bailey).

The authors have been very successful in presenting a survey of knowledge within these special fields, and are to be congratulated upon the excellency of their products. With the increase in interest in the rôle of proteins and amino acids in the physiologic economy of the body this volume should find a wide audience.

H. V.

**VITAMINS AND HORMONES. Advances in Research and Applications.** Edited by ROBERT S. HARRIS, Associate Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, and KENNETH V. THIMANN, Associate Professor of Plant Physiology, Harvard University. Vol. 2. Pp. 514; numerous figs. and tables. New York: Academic Press, 1944. Price, \$6.80.

THE editors have maintained the high standard of choice of topics and contributors that was evident in Volume 1 of this series of Reviews. The subjects covered, and the authors are as follows: (1) The Role of Vitamins in the Anabolism of Fats, by E. W. McHenry and M. L. Cornett; (2) The Chemistry of Biotin, by D. B. Melville; (3) The Nutritional Requirements of Primates other than Man, by P. L. Day; (4) Physiological Action of Vitamin E and Its Homologues, by K. E. Mason; (5) The Chemistry and Physiology of Vitamin A, by I. M. Heilbron, W. E. Jones, and A. L. Bacharach; (6) Para-Aminobenzoic Acid—Experimental and Clinical Studies, by S. Ansbacher; (7) A Critique of the Etiology of Dental Caries, by G. J. Cox; (8) Vitamins and Cancer, by D. Burk and R. J. Wenzler; (9) Effect of Androgens and Estrogens on Birds, by A. S. Parkes, and C. W. Emmens; (10) Hormones in Cancer, by E. C. Dodds; (11) X-ray Crystallography and Sterol Structure, by D. Crowfoot.

These critical reviews and condensations of the literature, by recognized leaders, should find a welcome place in the libraries of investigators interested in Nutrition and Physiology.

H. V.

**SURGICAL DISORDERS OF THE CHEST. Diagnosis and Treatment.** By J. K. DONALDSON, B.S., M.D., F.A.C.S., MAJOR, M.C., A.U.S.; Diplomate, American Board of Surgery; Associate Professor of Surgery and in charge of Thoracic Surgery, University of Arkansas School of Medicine, etc., Surgical Staff, St. Vincent's Infirmary and Visiting Staff, Baptist Hospital, Little Rock, Ark.; Formerly Chest Surgeon to Arkansas State Hospital for Nervous Diseases; Associate Surgeon, Robert B. Green Hospital, Visiting Surgeon to Santa Rosa, Nix, and Medical Arts Hospital, San Antonio, Texas. Pp. 364; 127 figs. Philadelphia: Lea & Febiger, 1944. Price, \$6.50.

THIS is a thoroughly practical volume presenting a comprehensive survey of the rapidly advancing field of thoracic surgery with its many ramifications. The author has recognized the need of general practitioners and general surgeons, as well as students and residents, for an epitomized volume dealing with fundamental advances in this field, many of which have not as yet

appeared in book form. The volume is roughly divided into 3 parts. The first comprises an excellent section on chest injuries and their management. The second section deals with intrathoracic infections, tumors and congenital abnormalities. Included in this portion of the work are chapters on the surgery of various cardiac disorders, and the problem of pulmonary embolism. The last section deals with the surgery of pulmonary tuberculosis. The text is written critically. The bibliography is ample and the illustrations well chosen and numerous. In the Reviewer's opinion it is a very much worthwhile book. L. S.

**HEART DISEASE.** By PAUL DUDLEY WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician to the Massachusetts General Hospital, Boston. Third Ed. Pp. 1025; 138 ills. New York: Macmillan, 1944. Price, \$9.00.

THIS 3rd edition is illustrative of the author's characteristic care in the thorough way in which he has revised an already excellent book to keep it up to date in a constantly advancing subject. And then to leave no stone unturned, he adds an addendum of chapter by chapter additions "inadvertently neglected." His new chapter on the range of the normal heart will be useful to all, and especially valuable to those who tend to set up rigid normal figures for a normality that spreads over wide ranges. Many a figure that is normal for one may be clearly abnormal for another individual. A pleasant and useful feature that could well be imitated in other American textbooks is the inclusion of perspective-giving historical sidelights and an appendix of cardiac chronology (omitted from the 2nd edition).

Dr. White's long-held authoritative position in American cardiology is further enhanced by this clearly written, well-presented, well-illustrated volume.

E. K.

## NEW BOOKS

*Colloid Chemistry.* Theoretical and Applied. By SELECTED INTERNATIONAL CONTRIBUTORS. Collected and Edited by JEROME ALEXANDER. Vol. 5. Theory and Methods, Biology and Medicine. Pp. 1256; numerous figs. and tables. New York: Reinhold, 1944. Price, \$20.00.

*Photoelements and Their Application.* By DR. BRUNO LANGE, Consulting Engineer, Berlin-Dahlem, Formerly Research Physicist with Kaiser Wilhelm Institute, Berlin. Translated by ANCEL ST. JOHN, PH.D., New York. Pp. 297; 67 figs. New York: Reinhold, 1938. Price, \$10.00.

*Medico-legal Blood Group Determination.* Theory, Technique, Practice. By DAVID HARLEY, M.D., B.Sc., F.I.C., The Laboratories of the Inoculation Department, St. Mary's Hosp., London. Second Impression. Pp. 119; 13 figs. New York: Grune & Stratton, 1944. Price, \$3.50.

*The Amino Acid Composition of Proteins and Foods.* Analytical Methods and Results. By RICHARD J. BLOCK, PH.D., Associate in the Department of Physiology and Biochemistry, New York Med. Coll.; Research Director, C. M. Armstrong, Inc., New York City; Formerly Research Associate in Chemistry, New York State Psychiatric Institute and Hosp., New York City; Consultant in the Chemistry of Proteins and Amino Acids; and DIANA BOLLING, B.S. Pp. 396. Springfield, Ill.: Thomas, 1945. Price, \$6.50.

*The Photochemistry of Gases.* By WILLIAM ALBERT NOYES, JR., Professor of Chemistry, Univ. of Rochester, and PHILIP ALBERT LEIGHTON, Professor of Chemistry, Stanford Univ. Pp. 475; 66 figs. New York: Reinhold, 1941. Price, \$10.00.

*Arterial Hypertension.* Its Diagnosis and Treatment. By IRVINE H. PAGE, M.D., and ARTHUR CURTIS CORCORAN, M.D., Research Division of the Cleveland Clinic Foundation, Cleveland; Formerly Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis. Pp. 352; numerous figs. Chicago: Year Book Publishers, 1945. Price, \$3.75.

*Shoulder Lesions.* By H. F. MOSELEY, M.A., D.M., M.Ch. (Oxon.), F.R.C.S. (Eng. and C.), F.A.C.S., Montreal, Canada; Lecturer in Surgery, McGill Univ.; Assistant Surgeon, Royal Victoria Hosp. Pp. 181; 70 figs. Springfield, Ill.: Thomas, 1945. Price, \$4.50.

### NEW EDITIONS

*Internal Medicine.* Its Theory and Practice. In Contributions by American Authors. Edited by JOHN H. MUSSEY, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane Univ. of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hosp., New Orleans, La. Fourth Ed. Pp. 1518; numerous figs. Philadelphia: Lea & Febiger, 1945. Price, \$10.00.

*Fischerisms.* Being a sheaf of sundry and divers utterances culled from the lectures of MARTIN H. FISCHER, Professor of Physiology in the Univ. of Cincinnati. By HOWARD FABING. This 3rd Edition by RAY MARR. Pp. 83. Springfield, Ill.: Thomas, 1944. This volume is a private print for his students.

"FOURTEEN years have elapsed since the first edition of *Fischerisms*. Many students who had the privilege of sitting at your feet these past years, have wanted but could not obtain the volume. In this time new aphorisms were jotted down upon our notebooks, many more upon the tablet of our memory."

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1945

## ORIGINAL ARTICLES

### COMPLICATIONS ARISING IN DONORS IN A MASS BLOOD PROCUREMENT PROJECT

By MARY HEISS BOYNTON, M.D.

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AND

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THE Blood Donor Service of the American Red Cross has been in operation since February, 1941. As of April 1, 1944, over 7,000,000 pints of blood have been collected from volunteer donors throughout the United States to be processed into dried plasma and serum albumin for the Armed Forces. This amount of blood represents donations from approximately 3,500,000 individuals, since the re-donor rate is now about 50%. The average weekly bleedings obtained approximate 103,000; the various Centers, depending on their respective capacities, handle from 1500 to 9000 donors weekly.

It is immediately obvious that an unprecedented opportunity is presented to compile and analyze the effects of this mass blood procurement project on the donors and to note especially the complications and problems attendant upon such a program. It has been the customary procedure, since March, 1942, to require that each Donor Center file with the National Office a monthly report which includes, along with the general statistics, a report of the reactions, complications, and accidents that have occurred during the previous month. Previous to that time, when only a very few Centers were in operation, detailed reports of all complications and accidents were filed by letter in the National Office as they occurred. From these reports, as well as from several special studies noted below, this survey has been made. In view of the increasing general interest in blood banks, especially for smaller hospitals and institutions, it is hoped that this report may be of some value to those concerned with the organization of such blood banks and may aid in anticipating some of the problems which arise from time to time in the maintenance of such projects.

The first consideration of the Blood Donor Service has been the care

and protection of the donor; the second has been the care and prevention of spoilage in the blood obtained. The achievement of the first objective must be based on 2 factors: (1) a controlled basis of operations throughout; (2) a rigid eligibility standard for all donors.

The methods of operation and the donor requirements have been discussed in previous papers.<sup>8</sup>

It has been the experience of the Blood Donor Service that the accidents and complications which may occur can be classified roughly into 4 groups: (1) those related to the mechanics of the venepuncture, and including those occurring during the examination and preparation of the donor; (2) those occurring as a general systemic reaction and including all consequences thereof; (3) those occurring as late, delayed, or prolonged reactions; (4) those occurring as coincidental or unrelated accidents, but approximating the time of the donation.

**Group 1.** The complications and accidents under this heading, with the exception of hematomata, constitute the smallest group. The number of reactions at this point in the procedure has considerable bearing on the personalities and techniques of the personnel handling the donors. As would be expected, there have been a few individuals who, through fright or nervousness, have fainted when the finger was pricked for a hemoglobin test, or who have bitten the thermometer when the temperature was taken. Reactions at this point of the procedure apparently have little or no adverse psychologic effect on other donors awaiting their turn.

Of the more serious incidents, there were 2 reported instances of infected fingers following punctures for hemoglobin determinations and 1 reported case of a felon followed by an osteomyelitis of the terminal phalanx of the finger.

In the preparation of the arm, soap, water, aqueous iodine (2%), and alcohol are used. The possibility of iodine burns is therefore slight. A 1% solution of novocaine or procaine-HCl has been used routinely as a local anesthetic prior to the insertion of the 15 gauge needle into the vein. In this connection 3 unfortunate, though not serious, incidents have occurred. In one Center, the use of a commercially-prepared solution of a local anesthetic, other than those referred to above, resulted in the formation of a small (1 cm.) area of local ulceration and subsequent slough. Use of the solution was promptly discontinued. In another Center, 1% sodium hydroxide was inadvertently substituted for novocaine in filling containers for sterilization. A similar error was made in the third case when 1% merthiolate was prepared in place of novocaine. Local reactions, similar to those noted in the first instance, resulted, all of which healed promptly with appropriate therapy. A few cases of a local reaction to novocaine have been reported.

A small number of individuals have exhibited a local sensitivity to the resin in the adhesive dressing which is used in most of the Centers to cover the site of the venepuncture. This has been especially noticeable among individuals who have neglected to remove the dressing at the end of the specified 24 hours.

Complications attendant upon the actual venepuncture comprise the majority of difficulties in the first group. No matter how skilled the operator, there will be technical difficulties which will result in a certain minimum number of complications directly related to the mechanical procedure of the venepuncture. It has been the policy of the Blood Donor Service to accept all donors, regardless of whether or not suitable veins were apparent. In approximately 1% of the donors the venepuncture has been classed as "unsuccessful" (*i. e.*, less than 350 cc. of blood has been obtained). Venepunctures are done by physicians or by nurses trained and qualified in this technique. It is a rule that no donor is "stuck" more than twice, regardless of whether one or both arms are used, and the venesection is discontinued whenever it is apparent that a large hematoma may develop. In this latter case the donor is informed that the arm may be discolored and painful, and is advised as to the symptomatic treatment required.

In a study of 40,000 donors, which is summarized in Table 3 and which will be reported in detail below, 10% of the donors indicated some pain, soreness, and/or discoloration in the arm from which the blood was withdrawn. These complaints ranged from slight discoloration or discomfort to an inability to use the arm for several days or more. This complication is unfortunate and often disturbing from the donor's point of view, but aside from a few instances, the discomfort has been minor and temporary. A number of cases have been reported in which the donors have complained of severe, persistent pain on motion of the elbow or shoulder at intervals varying from a few days to several weeks after the blood was withdrawn. In 8 of these cases, a definite diagnosis of bursitis was made, either radio-humeral, olecranon, or subdeltoid, depending on the location. In all of these cases a hematoma had existed prior to the development of the symptoms, and in 3 of the cases in which an actual bursitis developed, and in which calcium deposits were noted on Roentgen ray, a previous history of the same condition in the same joint was obtained. It is probable that the donor's natural reluctance to use the arm, following the development of the hematoma, aggravated a previously existing condition. In other cases the actual deposit of blood around the joint resulted in symptoms closely simulating a true bursitis. A few cases have been noted in which a complaint of severe pain in the arm or shoulder developed subsequent to a hematoma and in which Roentgen ray of the joint involved indicated a preëxisting hypertrophic arthritis with similar radiographic changes in the corresponding joint of the other arm. Here again the natural limitation of motion coincident with the existing hematoma undoubtedly aggravated an underlying subclinical condition. In 1 or 2 of the cases exhibiting these symptoms, the diagnosis of hysteria must be considered, in that no explanation for the prolonged discomfort could be found on repeated examination and Roentgen ray.

In the experience of the Service to date, there have been approximately 15 reported instances of a local abscess formation at the site of the venepuncture, in addition to those noted above as a result of

a faulty local anesthetic, and 3 reported cases of acute cellulitis of the inner aspect of the arm above the fossa. There have been 13 reported cases of a thrombophlebitis of one of the veins of the antecubital fossa, 1 of which was migratory through several branches of the median basilic vein over a period of several months. In addition there have been 2 cases of migratory phlebitis originating in the vein from which the blood was withdrawn and later involving the leg veins. In 1 of the latter cases the donor had had a previous history of thrombophlebitis. One donor developed a transient staphylococcus septicemia 48 hours after donation. He recovered after being hospitalized for 5 days.

**Group 2.** In this group the majority of reactions that occur can be classed as "faints" with a subheading of "the consequences thereof." Syncope in blood donors has been and probably always will be a major problem in any donor organization. Careful selection and examination of each individual donor as well as a reassuring attitude on the part of all personnel in direct contact with the donor will do much to lessen the apprehension with which many individuals approach a blood donation for the first and even successive times. In spite of these precautions a certain percentage of donors will have some form of reaction ranging from a mild presyncope to a true shock. Various estimates have been made of this percentage. Poles and Boycott<sup>6</sup> state that 2.8% of 10,000 donors showed "true" syncope. A Report to the British Medical Research Council<sup>7</sup> gives a figure of 5.5%, using the term "faints" to include all donors in whom "the symptoms and signs associated with fainting were sufficient to delay or alter the normal procedure." A study of 16,000 volunteer Red Cross donors in Atlanta, Ga.,<sup>4</sup> gave a total syncope rate of 4.2%, whereas in a survey of 40,000 consecutive donors in 4 other large Red Cross Centers, a figure of 8.9% was obtained as indicating the number of donors who had *any* immediate reaction following the donation. This is a figure based on a subjective estimate by the donor and represents positive answers to the question, "Did you have any ill-effects immediately following the donation?"

A number of surveys have been made from time to time on Red Cross volunteer donors in an effort to obtain information on a number of factors which might have bearing on reactions of this type, and to determine what group of individuals will experience syncope under what conditions. The majority of the figures referred to below were collected in a punch-card survey made in 6 different Centers throughout the country. Identical forms, a sample of which is printed below (Fig. 1), were sent to these Centers and a total of 5032 cards were returned, in which there were 2294 reactors, and 2738 non-reactors used as controls. These cards were filled out by the regular nurses attending the donors during the venesections. A smaller survey on a somewhat different basis was made in a single center on 2521 donors, 570 reactors and 1951 controls.<sup>1</sup> The results on these 2 surveys have been combined as far as possible, and the conclusions listed in Paragraphs 1 to 13 below. There would appear to be so many factors involved and so many possibilities to be considered that

statistical results can hardly be considered accurate. However, certain impressions have been gained and certain generalities may be stated.

FIG. 1.—CARD REQUESTING INFORMATION

AMERICAN RED CROSS BLOOD DONOR SERVICE	
1-4	NAME _____ DATE _____ SERIAL No. _____
5	SEX _____
	AGE _____
	WEIGHT _____
7	Light _____
8	Medium _____
9	Heavy _____
6	Donation—No.
y	Previous fainting—yes
x	no
7	Occupation
y	Clerical, executive, professional
x	Manual
0	Housewife
1	Other, specify _____
	History
3	Recent illness, specify _____
4	Menstruation—absent
5	present
6	week before or after
7	other part of cycle
8	History of fainting
9	of convulsions
8	Psychologic Factors
1	Friend or relative in Armed Service
2	Reaction of friend to donation
3	Other faints in room
4	Prolonged wait before donations
5	General apprehension
6	Ease of venesection
7	Other pertinent history
9	Last food—hrs. since _____
y	heavy meal
x	prescribed food
10	Work—hrs. since _____
11	Work
1	light
2	hard
3	indoor
4	outdoor
12	Last sleep—hrs. since _____
13	duration in hrs. _____
14	Type of Reaction
1	None
2	Mild or transient
3	Prolonged with minor symptoms
4	Severe collapse
15	Point of Reaction
0	Before donation
1	In bleeding room—before
2	during bleedings
3	after bleeding
4	In canteen—before eating
5	after eating
6	hot nourishment
7	cold nourishment
8	smoking
9	Delayed—specify place
16	Amount bled _____ cc.
17	Symptoms
y	Pallor
x	Perspiration
0	Loss of consciousness
1	Nausea
2	Vomiting
3	Cramps
4	Twitching
5	Tetany
6	Incontinence
7	Hysteria
8	General convulsions
9	Other, specify _____

The reverse side of the card provided space for entries on the donor's temperature, pulse, and blood pressure, and for outside temperature, barometric pressure, and humidity.

1. *Classification.* All reactions were classified as (1) mild or transient, (2) prolonged or severe. Loss of consciousness was not felt to be an adequate basis for distinguishing a mild from a severe reaction. A donor may lose consciousness momentarily, yet recover so rapidly that the reaction may be considered transient, whereas another donor may appear initially to have only a mild presyncope, but ultimately develops a reaction that is unduly prolonged and alarming. The group classed as "severe" includes all donors who have exhibited generalized convulsions with or without tetany. In general, mild or transient reactions comprise 88% of the total, and the severe reactions, 12%. The same grades of reactions are apparent in both new and redonors.

2. *Sex.* The ratio of males to females in those who react is about 1:1.5; the ratio of males to females in the entire donor group is 4:5.

3. *Age.* The proportion of reactions is highest in females under 21 years. Under 40 years of age in both males and females reactions



were higher in proportion to the total number of donors than in the group over 40 years of age (*i. e.*, 71% of the reactions occurred in 61.2% of the donors under 40 years of age). The more severe grades of reactions, however, occur more frequently in the older age groups.

4. *Number of Donations.* The incidence of reactions is from 3 to 4 times greater in first donors than in redonors. This is to be expected, both because of self-selection and because donors who have had a marked reaction are requested not to return.

5. *Weight and Body Build.* In both male and female donors weighing under 120 pounds the incidence of reactions is about twice the usual expectancy; this ratio diminishes gradually until, over 150 pounds the actual ratio is less than the expected. About half of the "severe" reactions occur in so-called "light females." In the entire donor group, 56% of all first donors were classified as "light," whereas in the redonor group only 15% were in this category, which would indicate a certain degree of self-selection, considering the fact that approximately 80% of all reactions occur in the first-time donors.

6. *Occupation.* Among males in the so-called "white collar class," the proportion of reactors is slightly higher than among the other groups; the same is true for women. There is slight evidence to indicate that those who are normally engaged in strenuous physical labor are less likely to develop reactions.

7. *Temperature, Humidity, Time-of-day.* The impression is widespread that more reactions occur on warm, humid days; this cannot be confirmed statistically. However, on any day in which there has been a sudden change in the temperature, the number of reactions is noticeably increased. There is slight evidence to indicate that there are fewer reactions during the morning hours; this, of course, is linked closely with the increasing fatigue of the later hours of the day.

8. *Food, Rest, and Sleep.* There is no statistical correlation as to these factors among those who react. Only in the extreme cases does lack of food or sleep appear to have any bearing on the development of a reaction.

9. *Blood Pressure and Pulse Rate.* There appears to be little correlation between the pulse rate and those who react, as opposed to those who do not. There is definite evidence to indicate that hypotension predisposes to reactions. With systolic values less than 110 mm./Hg before donations, the incidence of reactions is  $2\frac{1}{2}$  times greater than was to be expected.

10. *History of Fainting.* This is an important predisposing factor among those who react. In a group of 5000 donors, 18% of the reactors and only 3% of the non-reactors had a history of fainting under other circumstances.

11. *Psychologic Factors.* One of the outstanding factors predisposing to syncope is apprehension. In the group noted in Paragraph 10 above, 7% of the controls admitted to or showed apprehension prior to the donation, whereas this was noted in 30% of those who reacted. This finding is equally true for men and women, and, as would be expected, is overwhelmingly characteristic of first donors. The pres-

ence of other reactions in the room is a disturbing factor twice as often in the reactors as in the non-reactors.

12. *Point of Reaction.* About 1% of all reactions occur before the donor enters the bleeding room; 50% occur in the bleeding room during the donation; 20% in the bleeding room after the donation; the remaining 29% occur while the donor is in the canteen or preparing to leave the Center. It is of interest to note that in this latter group, reactions are 10 times as frequent following hot nourishment, such as coffee as after other liquids. This, however, is undoubtedly explained by the fact that the majority of donors will take coffee following the donation in preference to other liquids offered. The incidence of delayed reaction, *i. e.*, outside the Center, is about 0.1%.

13. *Symptoms.* The symptoms encountered are listed below in order of frequency as determined in one series of 2294 "reactors." A combination of symptoms occurred, of course, in many of the donors. It is of interest to note that the more severe symptoms encountered, such as loss of consciousness, nausea, vomiting, convulsions, and tetany, occur more frequently in women.

TABLE 1.—SYMPTOMS ENCOUNTERED IN SYNCOPE IN ORDER OF FREQUENCY

	Total, 2294		Males, 927		Females, 1367	
	No.	%	No.	%	No.	%
Pallor . . . . .	2139	93.24	887	95.69	1252	91.59
Perspiration . . . . .	1588	69.22	722	77.89	866	63.35
Nausea . . . . .	638	27.81	210	22.65	428	21.31
Loss of consciousness . . . . .	253	11.03	92	9.92	161	11.78
Vomiting . . . . .	105	4.57	20	2.16	85	6.22
Convulsions . . . . .	78	3.40	25	2.70	53	3.88
Twitching . . . . .	48	2.09	16	1.73	32	2.34
Cramps . . . . .	43	1.88	11	1.19	32	2.34
Tetany . . . . .	22	0.95	6	0.65	16	1.17
Incontinence . . . . .	11	0.47	4	0.43	7	0.51

All of the above generalizations agree with the findings in the British Report to the Medical Research Council referred to above. An attempt to draw any statistical conclusions on either the constitutional or physical factors which predispose to fainting is difficult. Aside from the obvious fact that a history of previous fainting and an admission of apprehension on the part of the donor predisposes to a reaction, definite conclusions may not be drawn. The impression is obtained that fainting in donors is probably associated with a certain psychosomatic pattern, but the difficulties of evaluating this in a large series of volunteer blood donors have thus far prevented any study of this possibility.

There have been approximately 34 donors who have exhibited symptoms and signs of shock sufficiently severe to require hospitalization for observation and, on a number of occasions, it has been deemed wise, in the judgment of the physician-in-charge at the Center, to auto-transfuse donors who have had a severe reaction, in order to forestall the development of a more serious situation. All donors who have exhibited any reaction which would be classified as severe have been advised to make no further blood donations.

The widespread use of aromatic spirits of ammonia as a restorative in all Centers has required that special precautions be taken in its use. Six instances are reported in which the solution has inadvertently entered the donor's eye. Prompt washing out of the eye and the use of neutral ammonium tartrate (10%) alternating with 1% pantocaine prevented any serious damage.

The problem of syncope among blood donors is magnified by the accidents which may occur when syncope precedes or is accompanied by a fall. The accidents which have occurred under such circumstances are listed below:

- (a) Scalp and head lacerations (108)
- (b) Abrasions elsewhere (32)
- (c) Basal skull fracture (2)
- (d) Mandibular fracture (3)
- (e) Fracture of nose (5)
- (f) Fracture of malar bone (1)
- (g) Fracture of finger (2)
- (h) Fracture of clavicle (3)
- (i) Fracture of olecranon process (1)
- (j) Chipped teeth (18)
- (k) Sprained ankle (4)
- (l) Mild concussion (14)

Of all the complications which may occur coincident with or following a blood donation, cardiovascular accidents are the most disturbing. Individuals who present themselves for a blood donation, either as volunteers or professionals, are a selected group from two aspects. There is a high degree of self-selection in that the majority of these individuals know, or believe themselves to be, in reasonably good health. In addition, the history taken and the brief examination performed should eliminate all those who show any evidence of acute infection or of serious chronic disease, as well as those who by general health standards would be ineligible. It is undoubtedly true that the response of prospective donors to the questions asked may be inaccurate for a variety of reasons and it will be noted below that an evasive response on the part of the donor to the questions asked can assume major significance. Because the responsibility cannot be transferred, it has been the policy of the Service not to accept, on the basis of an outside physician's recommendation or request, any donor who does not meet the physical requirements as set up. This is of particular importance in the appraisal of donors with hypertensive cardiovascular disease.

No deaths attributable to cardiovascular causes have occurred in any Donor Center or at any Mobile Unit Station. The 10 deaths which have occurred within 48 hours of the donation are noted in detail in Table 2. It will be seen that in 5 of these cases a history of cardiovascular disease had existed but was denied by the donor at the time of examination. In all but 2 instances (Nos. 6 and 10), there was no indication before donation that the cardiovascular system might be suspect. Case 6 should not have been accepted as a donor on the basis of the predonation blood pressure; Case 10 was a 7-time donor;

TABLE 2.—FATAL CARDIOVASCULAR ACCIDENTS

No.	Center	Date	Sex	Age	Previous donations	Findings before donation				Immediate reaction	Onset of symptoms	Outcome	Diagnosis	Remarks
						T.°	P.	B.P.	History					
1	A	4/21/43	M	50	1	98.4	78	160/90	Neg.	No	App. 6 hrs.	D. within 12 hrs.	Prob. coron. thromb.	
2	A	6/21/43	F	54	0	98.0	72	118/80	Neg.	No	App. 6-8 hrs.	D. ?	"	Made 100 mile trip home after donation; collapsed, died several hours later
3	B	7/43	F	44	2	98.6	80	120/70	Denied	No	4 hrs.	D. 12 hrs.	"	Family history of angina; donor had had previous attacks—denied history, later admitted by family
4	C	1/15/43	M	46	0	98.8	104	136/78	Neg.	Slight	4-5 hrs.	D. 5 hrs.	"	Autopsy diag.; coronary sclerosis and acute cardiac dilatation
5	D	8/25/43	M	46	0	98.2	84	134/80	Neg.	No	12 hrs.	D. 16 hrs.	"	
6	D	'43	M	48	1	98.0	86	202/128	Denied	No	48 hrs.	D. 48 hrs.	"	Previous history of "heart attacks" denied at time of examination
7	E	6/43	M	48	?	?	?	150/90	Denied	No	?	D. 48 hrs.	Cereb. hem.	History of treatment for hypertension obtained later
8	F	11/27/43	M	53	?	97.0	72	170/80	Denied	No	24 hrs.	D. 24 hrs.	Prob. coron. thromb.	Donor went bowling immediately after donation—had history of cardiac episodes, denied at time of examination
9	F	2/29/44	F	50	?	98.8	104 irreg.	140/80	Denied	Slight	3 hrs.	D. 72 hrs.	Cereb. hem.	History of treatment for hypertension; denied at time of examination
10	G	9/ 3/43	M	58	7	97.4	78	186/106	Neg.	No	Within 8 hrs.?	D. within 8 hrs.?	Prob. coron.	Not investigated

TABLE 3.—NON-FATAL CARDIOVASCULAR ACCIDENTS

No.	Center	Date	Sex	Age	Previous donations	Findings before donation				Immediate reaction	Onset of symptoms	Diagnosis	Outcome	Remarks
						T.°	P.	B.P.	History					
1	F	1/ 3/44	M	48	?	96.8	88	148/90	Neg.		During donation	Angina	Rec.	
2	H	12/13/43	M	47	1	98.8	110	148/90	Neg.	Slight	1 hr.	Left hemipl.	Rec.	
3	D	11/ 5/43	F	54	?	98.6	88	180/120	Denied	No	2 hrs.	Cereb. acid.	Rec.?	Actual age not known—well over 60; hospitalized 2 weeks; hosp. diagnosis, "acute congestive heart failure"; history of chronic myocarditis
4	D	2/19/42	F	57*	No	97.4	108	180/100	Denied	No	1 hr.	Card. failure	Rec.	
5	A	8/6/42	M	47	No	98.4	96	172/112	No		During donation	Cereb. acid. left hemipl.	Rec. (slow)	Over age—accepted on recommendation of his own physician—such exceptions not permitted now.
6	A	5/42	M	63	No	98.6	88	150/106	Neg.		During donation	Coronary thrombosis	Rec.	Had history of previous cardiac episodes; denied at time of examination
7	A	3/25/43	M	46	?	97.8	92	160/100	Denied		During donation	Angina	Rec.	
8	J	12/13/43	M	45	1	98.0	110	140/90	No	No	2 hrs.	Cereb. acid. left hemipl.	Rec.	

exceptions have occasionally been made (for diastolic pressures over 100) in cases of this type.

Table 3 lists those cardiovascular accidents, occurring within 48 hours of the donation, in which the outcome was not fatal. It is entirely possible that an occasional unreported episode of this nature has occurred in addition to those noted. It will be seen that 4 of the 8 instances reported were cerebral accidents in contrast to the fatal group, in which only 2 of 10 were cerebral accidents. In addition, the onset of symptoms occurred during the bleeding in half of the non-fatal group, as contrasted with none in the fatal group.

In a group as large as that constituted by the donors (approximately 3,500,000 individuals) and encompassing the age distribution of such a group, a number of sudden deaths would be expected to occur within a period of 48 hours. It is, however, impossible to estimate how many might have occurred both because of the selection in the group and because detailed information is not available for this donor population on a number of other factors which influence mortality. However, on the basis of the nearest comparable standards derived from life insurance experience, the number of deaths that have been reported within 48 hours is considerably less than would be reasonably expected to occur, especially if it is taken into consideration that in 5 of the 10 deaths reported, the factor of selection did not operate because of incorrect answers to questioning.

**Group 3.** According to the card survey summarized in Table 4, approximately 4% of all individuals who donate blood experience some limitation of their activities during the week following the donation. There are, however, only rare instances reported of individuals who complained of weakness and lassitude for longer than 1 week. On thorough examination of most of these latter individuals it would appear that there was no physical basis for the persistence of symptoms and that these complaints were probably psychogenic in origin.

It has been the feeling of those closely connected with the medical aspects of the Service that the 4% of individuals noting prolonged lassitude following a donation consisted chiefly of those women who may not have regenerated their hemoglobin with normal rapidity. Until recently, a Tallqvist hemoglobin determination was made on all donors. Extensive investigative work<sup>2</sup> in several of the Centers revealed a fairly high percentage of error in the use of this method, especially in women whose hemoglobin was around the critical range of 80%. During the course of this work it was noted that a group of 220 women donors accepted for their first donation with a hemoglobin *over* 12.5 gm., determined by photo-electric cell colorimeter, did not show a diminution in their average hemoglobin at the time of their second or of their third donation. It may therefore be assumed that if an adequate hemoglobin level (accurately determined) exists at the time of the first donation, the problem of hemoglobin regeneration in women donors should be markedly lessened. As a result of this work, which will be reported shortly, the copper sulfate method of Phillips and Van Slyke<sup>5</sup> was instituted as a routine procedure for hemo-

globin determinations in all Centers. It is hoped that the widespread use of this method will eliminate the majority of those whose accep-

TABLE 4.—ANALYSIS OF INFORMATION RECEIVED												
Center A			Center B			Center C			Center D			Total
9,665 - (Nov.-Feb.)			10,000 (Feb.-July)			10,000 (Dec.-March)			9,977 (April-July)			39,642
7,246 - (75.0%)			5,577 - (56.8%)			6,488 - (64.9%)			7,612 - (76.3%)			27,021 - (68.2%)
Percent of:			Percent of:			Percent of:			Percent of:			Percent of:
Total			Total			Total			Total			Total
Returned			Returned			Returned			Returned			Returned
Out			Out			Out			Out			Out
No. of			No. of			No. of			No. of			No. of
Cards			Cards			Cards			Cards			Cards
6087			4472			5027			6453			22047
84.0			78.8			77.5			84.9			81.6
53.0			44.7			50.3			64.8			55.6
12.0			21.2			22.5			15.1			12.5
1159			1205			1461			1149			4974
16.0			12.1			14.7			11.5			18.4
Cards on which no complaint was noted			Cards register- ing any complaint or comment			Cards register- ing any complaint or comment			Cards register- ing any complaint or comment			12.5
Analysis by type of complaint*			Analysis by type of complaint*			Analysis by type of complaint*			Analysis by type of complaint*			Percent of:
Type 1 only			Type 1 only			Type 1 only			Type 1 only			Percent of:
457			457			457			457			Percent of:
454			454			454			454			Percent of:
51			51			51			51			Percent of:
87			87			87			87			Percent of:
60			60			60			60			Percent of:
28			28			28			28			Percent of:
22			22			22			22			Percent of:
1, 2 and 3			1, 2 and 3			1, 2 and 3			1, 2 and 3			Percent of:
No. of			No. of			No. of			No. of			Percent of:
Cards			Cards			Cards			Cards			Percent of:
1378			1529			1912			1395			Percent of:
100.0			100.0			100.0			100.0			Percent of:
45.4			37.8			10.2			9.6			Percent of:
42.9			45.9			12.4			11.9			Percent of:
11.7			2.2			4.4			8.0			Percent of:
Total complaints			Total complaints			Total complaints			Total complaints			Percent of:
Type 1			Type 1			Type 1			Type 1			Percent of:
2			2			2			2			Percent of:
3			3			3			3			Percent of:
161			161			161			161			Percent of:
Total complaints			Total complaints			Total complaints			Total complaints			Percent of:
1378			1529			1912			1395			Percent of:
100.0			100.0			100.0			100.0			Percent of:
45.4			37.8			10.2			9.6			Percent of:
42.9			45.9			12.4			11.9			Percent of:
11.7			2.2			4.4			8.0			Percent of:
Total complaints			Total complaints			Total complaints			Total complaints			Percent of:
1378			1529			1912			1395			Percent of:
100.0			100.0			100.0			100.0			Percent of:
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11.7			2.2			4.4			8.0			Percent of:
Total complaints			Total complaints			Total complaints			Total complaints			Percent of:
1378			1529			1912			1395			Percent of:
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1378			1529			1912			1395			Percent of:
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11.7			2.2			4.4			8.0			Percent of:
Total complaints			Total complaints			Total complaints			Total complaints			Percent of:
1378			1529			1912			1395			Percent of:
100.0			100.0			100.0			100.0			Percent of:
45.4			37.8			10.2			9.6			Percent of:
42.9			45.9			12.4			11.9			Percent of:
11.7			2.2			4.4			8.0			Percent of:
Total complaints			Total complaints			Total complaints			Total complaints			Percent of:
1378			1529			1912			1395			Percent of:
100.0			100.0			100.0			100.0			Percent of:
45.4			37.8			10.2			9.6			Percent of:
42.9			45.9			12.4			11.9			Percent of:
11.7			2.2			4.4			8.0			Percent

justifiable reason for a complaint of prolonged lassitude and weakness.

It is of interest to note that the donation of 500 cc. of blood may have a variable effect on the menstrual cycle in women. There have been a few complaints of an excessive or prolonged period shortly following a donation; the majority of women who make any note of an irregularity report a delayed or scanty period. It has not been possible as yet to correlate this information with hemoglobin values existing at the time.

It has been a rule in the Blood Donor Service not to accept anyone as a donor who has had a history of malaria within the preceding 15 years, not because of the possibility of a transmission of the infection, as this has been shown to be most unlikely,<sup>3</sup> but because of the possibility of the reactivation of a long-dormant infection in the donor. In this connection an interesting example of a late or delayed reaction was found in a donor who, although he had had a history of malaria 7 years previously with subsequent relapses, answered in the negative when asked that question. After his second donation he called the Center and inquired as to why he had had chills and fever for several days following each donation. A further inquiry into his history was made, and the explanation for his "reaction" obtained; he was strongly advised to discontinue further donations.

**Group 4.** In a cross-section of the population as large and as varied as the donor group, it is obvious that certain situations will arise and certain accidents occur which will approximate the time of the blood donation, but will actually be coincidental and unrelated to the donation. These cases are of interest and concern to the Service chiefly because of the false rumors and misconceptions which they may initiate. As an example of this may be mentioned a female donor who complained of severe pain in the arm from which the blood was withdrawn shortly after the donation. A thorough examination of the donor, including Roentgen rays, at first revealed no basis for the complaint, although subsequent Roentgen rays some weeks later indicated an osteogenic sarcoma of the humerus. A similar coincidental relationship occurred in the case of a female donor who noted the onset of nausea, dizzy spells, and loss of memory shortly after a donation. A brain tumor was diagnosed shortly thereafter. Another donor died 48 hours after a blood donation, with a diagnosis of meningitis. As an example of a slightly different type of accident which may occur, the case history of one prospective donor is given below:

A female donor, age 24, reported at the Center for a blood donation at 1 P.M. on the appointed day. On examination prior to the donation, the following data were obtained: Temperature, 98.6°; pulse, 128; hemoglobin, 95%; blood pressure, 220/160. The history was otherwise negative. She was rejected because of the elevated blood pressure, and was preparing to leave the building when she complained of a pain in her head and fell to the floor with loss of consciousness. She struggled for a few seconds and then became moribund. The usual restorative measures were applied without success. Her family physician was notified and she was transferred by ambulance to a local hospital. She did not regain consciousness and died 9 hours after onset of symptoms.



This is the only incident of this type which has occurred. It is of importance not only because of the implications and repercussions which would have developed had this donor been bled, but also because of the fact that the incident serves to emphasize the necessity for a strict observance of the eligibility regulations for blood donors, especially as regards any history of and/or signs of cardiovascular disease.

Two cases are reported in which donors were said to have developed leukemia within 3 months of the donation. In both cases, examination of the donor was entirely negative at the time of the donation, and the development of that particular disease process can only be considered coincidental.

FIG. 2.—CARD REQUESTING INFORMATION

Date_____	M._____	F._____	Age_____	No._____
<p>You have generously donated your blood to the Armed Services. Will you kindly fill out and mail this card one week from the date of your donation?</p>				
<p>(1) Did you have any ill effects immediately after donating your blood?_____</p>				
<p>(2) Was the arm from which the blood was withdrawn sore, stiff, or markedly discolored?_____</p>				
<p>(3) Were you in any way limited in your activity during the week after you donated blood?_____</p>				
<p>(4) Remarks_____</p>				
<p>No Signature Needed</p>				

It is the customary procedure in all Centers to note on the donor's medical card whether or not that donor had a reaction at the time of the donation. It is ordinarily impossible, however, to obtain any accurate estimate of the donor's own reaction to the procedure, both as to any prolonged after-effects and as to the complications related to the mechanical procedure of withdrawal of the blood. To obtain such information, a card (Fig. 2) was given to 10,000 consecutive donors in each of four fixed Centers in various sections of the country. The donor was asked to mail the card back to the Center 1 week after the donation. The results are tabulated in Table 4.

It will be noted that out of 39,642 cards given out, 68.2% were returned. In analyzing the figures, it will be seen that the percentage of cards with complaints or comment in relation to the total returned is highest where the percentage of returned cards is the lowest. In relation to the cards given out, the percentage of cards with complaints or comments is much more uniform. It is a safe assumption, therefore, that the percentage with complaints among those not returning the cards is distinctly lower than among those returning the cards.

No attempt was made to separate the complaints on the basis of severity. The donor was permitted to make his own estimate of his reaction, and all complaints or comments noted were included in the final count, although many were obviously negligible. On this basis,

it will be noted that 8.9% of those who returned the cards noted some reaction immediately following the donation; 10.1% noted varying degrees of discomfort or discoloration in the arm from which the blood was taken; and 4.1% noted some limitation of their activities within the week following the donation.

Anyone who has had wide experience in hospital or private practice is well aware of the forms which "hysteria" may take, especially in individuals with hypochondriac tendencies. It might, therefore, be expected that in a project with such a high degree of emotional appeal, there might be many individuals who would attempt to attach a multitude of minor complaints to the fact that they had given a blood donation. Whether because of the high degree of self-selection automatically practiced by the donors or whether because of the coöperative impulse involved in donating blood, there have been few instances in which a justifiable reason has not existed for a donor's complaint.

**Summary.** 1. With a controlled basis of operations for all procedures and a rigid eligibility standard for all donors, the withdrawal of 500 cc. of blood from normally healthy individuals should offer no serious potential hazard to the donors. The experience of the American Red Cross Blood Donor Service to date has confirmed this assumption.

2. Approximately 10% of the 40,000 donors studied have (for technical reasons) experienced transient discomfort in the arm from which the blood was withdrawn.

3. Approximately 9% have experienced some form of a transient reaction during or immediately following the donation. This number is fairly constant in a general cross-section of the population in the age group selected, and is dependent on a variety of factors which are not constant. The instances of delayed reactions or syncope occurring some hours after the donation are rare. The symptoms encountered in order of frequency are listed.

4. The cardiovascular complications which have occurred are reported, but in view of the fact that the normal expectancy for accidents of this nature is far greater than the actual experience of the Service, regardless of whether or not the factor of selection is considered, it is impossible to conclude that these complications were directly related to the withdrawal of blood.

5. A certain number of individuals, approximately 4%, have experienced prolonged or late manifestations, the basis for which may have been a delayed regeneration of hemoglobin. Only a very small group has developed symptoms for which there is no apparent physical basis.

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## THE USE OF A "MODIFIED GLOBIN" FROM HUMAN ERYTHROCYTES AS A PLASMA SUBSTITUTE\*

### PRELIMINARY REPORT

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BLOOD is a very complex substance with numerous physiologic attributes. The thought of fractionating human blood and of using the various components for the purpose best suited appears natural and presumably occurred to many before our work was begun. In a letter of Captain Ward at the close of the last World War, plasma was suggested as a therapeutic means in the treatment of shock. Robertson actually used preserved red cells for the treatment of shock.

The practical application of fractionation of human blood to therapeutics does not appear to have gone any further before 1927. In that year we began fractionation of citrated blood by centrifugation. By this simple means blood can be divided into three portions: (1) Supernatant layer containing plasma and a portion of the platelets; (2) a buffy coat or leukocytic cream containing the bulk of the leukocytes and platelets; (3) a layer of underlying erythrocytes.

These three portions were administered from that time on to patients, and it soon became evident that the idea of blood fractionation suggested by *a priori* considerations was sound, practical and yielded good results. Although of these three portions plasma was used more extensively, the first outstanding results were obtained with the use of leukocytic cream, a fraction which has not received lately the attention that it deserves. The use of *citrated plasma* need not be discussed here.

The "*leukocytic cream*" has been suggested<sup>27</sup> as an effective bone

\* This paper is the 17th of a series on plasma and plasma substitutes from the Laboratory of Clinical Pathology of the Bryn Mawr Hospital. This work has been initiated with the aid of the Plasma Research Fund of the Bryn Mawr Hospital, and continued under contract with the Committee on Medicine of the National Research Council and from the Committee on Medical Research of the Office of Scientific Research and Development.

marrow stimulant in all cases of agranulocytosis not due to a severe myelophthasic or aplastic lesion. With the cases included in the first publication, a total of at least 26 cases of severe neutropenia (agranulocytosis) have been treated so far. Of these, 23 recovered and 3 died. All the fatal cases showed at autopsy a very severe hypoplasia of the bone marrow, a condition not generally present in agranulocytosis.<sup>7</sup> The predominant lesion in agranulocytosis is a defect in the mechanism of maturation of the granulocytic cells.

The *erythrocytes*, resuspended in salt solution, have been used occasionally by us and others in the treatment of acute and chronic anemias, usually of the posthemorrhagic type. More recently, with the large amounts of red cell residue left from the preparation of plasma for the Armed Forces, utilization of red cells for transfusion<sup>1a-j</sup> and for surgical dressing<sup>142,b</sup> has been emphasized. Presumably, with the finding of better methods of erythrocyte preservation than now available, suspension of erythrocytes left over from plasma preparation will find a definite place as a therapeutic agent. While, therefore, this work should continue, there are at present several limitations to a generalized use of red cell residue from plasma preparation. Some of the most important are: (1) In the majority of hospitals, plasma is prepared from blood which has been kept in the refrigerator to the limit of safe erythrocyte preservation. (2) When the red cells are the by-product of commercial plasma preparation, the area of distribution is naturally limited. (3) The safe limit of preservation of centrifuged resuspended cells is short. (4) Not all anemic patients are adequately treated with erythrocytes alone.

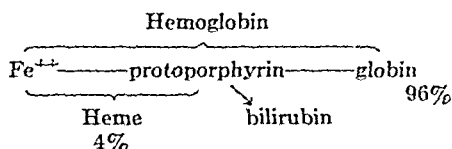
In addition to the unusually large amount of red cells now available from plasma preparation for the Armed Forces, there will always be the opportunity of utilization of large quantities of red cells which remain from the routine preparation of plasma in many hospitals throughout the country or from state wide organizations.

In this preliminary paper, evidence will be presented that a globin can be prepared from human erythrocytes which is safe and which has a wide field of application as a plasma substitute in the human. It is recognized that the expression "plasma substitute" is very confusing, there being no substance which has the same physicochemical and physiologic attributes of plasma. However, the term has been so widely used that one must accept it. It is used here in a limited sense to indicate a substance possessing some of the properties of plasma: more specifically, a high colloidal osmotic pressure. Because of this property and of other physicochemical properties, globin solutions can be successfully used to replace lost blood volume.

*Outline of Composition of Hemoglobin.* The hemoglobin content of normal human blood varies, but it is usually 14 to 16 gm. per 100 cc. Hemoglobin is very soluble in water, and consists of 3 components: iron, porphyrin and a protein, globin. Globin constitutes about 96% of the total hemoglobin. The structure of the porphyrin nucleus is fairly well known chemically. It consists of four pyrrole rings connected cyclically through carbon atoms.

There is some confusion in nomenclature, but the alkaline iron-porphyrin compound is usually known as alkali hematin or heme, while the acid hematin is known as acid heme.

When hemoglobin is broken down in the body, the 3 components are apparently split from each other. The iron is retained by the body for the formation of new hemoglobin. Some or all of the porphyrin, which has been identified as protoporphyrin, is converted to bilirubin. It may be assumed that the fate of the globin is similar to that of any other native tissue protein. The 3 components of hemoglobin can be separated chemically with relative ease. Mild treatment of oxyhemoglobin with acid readily cleaves the globin from the iron-porphyrin combination. Treating oxidized heme with a weak acid will give iron plus protoporphyrin.



*Preparation and Properties of Globins.* In 1871 Preyer<sup>16</sup> demonstrated that hemoglobin could be split into its two components of hematin and globin by treatment with a strong acid. This method of preparing relatively pure globin was used in 1898 by Schulz,<sup>24</sup> who pointed out that in the preparation of globin, the concentration of the acid used for the decomposition of hemoglobin was of primary importance. The final globin product was soluble in either dilute acids or alkalies but insoluble at its iso-electric point, which according to Osato<sup>15</sup> was at a slightly alkaline pH. The lethal dose of this globin to rabbits according to Schittenhelm<sup>23</sup> was 0.15 gm. In 1913 Robertson,<sup>18</sup> using essentially the methods of Schulz but with some small modifications, obtained 3 fractions of globin.

Other workers, notably Bertin-Sans and Mortissier,<sup>5</sup> Anson and Mirsky<sup>3</sup> and Barcroft,<sup>4</sup> using slight modifications of Schulz's procedure for the production of globin, showed that they were able to re-synthesize hemoglobin from the two products of hemoglobin cleavage. If this was so, then the globin obtained by them was probably not a denatured product as obtained by Schulz. Hill and Holden<sup>12</sup> stated that the globin as prepared by the Schulz method was a type of meta-protein such as is normally obtained when dilute acids acted upon albumins or globulins. These workers claimed to have obtained an undenatured globin by using a minimum quantity of acid to split the hemoglobin and by carrying out all procedures at 0° C. Haurowitz<sup>11</sup> has classified this globin as an albumose while Schenck<sup>22</sup> classed it as a transitional substance falling somewhere between basic peptone and histone.

Anson and Mirsky<sup>2</sup> incorporated the use of an organic solvent with acid for the preparation of globin. Hydrochloric acid solution in acetone was used for splitting hemoglobin. Roche<sup>19</sup> had found that at least 3 different globins were formed when hemoglobin was treated with acids, namely, native globin, fully denatured globin and an

intermediate substance insoluble at the iso-electric point which has been termed "paraglobin."

In this same period, Schenck<sup>22</sup> also outlined a method for globin preparation employing an acid acetone. The lethal dose of this globin in a 2.5 kg. rabbit was 0.75 gm., while doses up to 0.4 gm. were well tolerated.

Roche *et al.*<sup>21</sup> in 1932, working with globins prepared by the method of Hansik<sup>10</sup> and also of Anson and Mirsky, studied their stability and osmotic pressures. Their observations indicated that native globin was fairly stable, although the globin prepared by the method of Anson and Mirsky was relatively unstable even when kept at 0° C. Reiner *et al.*<sup>17</sup> found that the globin prepared by the method of Anson and Mirsky when analyzed electrophoretically consisted of 2 components: a "slow" component approximating about 40% of the material and a "fast" component consisting of approximately 60% of the material. A small fraction of purified globin prepared by 55% saturation with  $(\text{NH}_4)_2\text{SO}_4$  as proposed by Roche and Combette,<sup>20</sup> showed the same pattern after 2 weeks of continuous dialysis.

Gralen,<sup>9</sup> using the method of Anson and Mirsky for the preparation of soluble globin, found that the solutions obtained were never very stable. This observation was also made by Roche *et al.*<sup>21</sup> The molecular weight by Svedberg's formula was found to be 37,000 for globin. The latter is similar to that obtained by Steinhart<sup>26</sup> for the urea-hemoglobin solution.

The molecular weight of globin as determined by Svedberg<sup>25</sup> was of an indeterminate nature consisting of high molecular weight material ranging down to 17,000. He characterized hemoglobin as consisting of 4 globin units of 17,000 molecular weight each.

Roche *et al.*<sup>21</sup> stated that the molecular weight of globin obtained osmotically depended on the concentration of the protein solution being analyzed. It was possible at times to obtain a molecular weight for globin which was greater than that of hemoglobin.

*Summary of Literature.* A review of the literature indicates that a number of widely different "globins" can be obtained, according to the method of preparation, and that little, if any, pure "native" globin can be obtained with any of the methods proposed. The products so far obtained fall into three categories: (1) The denatured globin of Schulz, soluble in dilute acids and alkalis. Upon reconstitution with alkaline hematin it gives rise to a hemochromogen instead of methemoglobin. This material has been found to be toxic in relatively small doses when inoculated into rabbits. (2) The globin as prepared by Hill and Holden. This material, prepared at 0° C. without the use of alcohol, was found to be soluble over a pH range of 5 to 10 and appeared relatively stable. Upon resynthesis with alkaline hematin the characteristic band of hemoglobin was obtained. No toxicity studies were made with this globin. (3) The acid-acetone globin of Anson and Mirsky. This material has been the most widely studied. By means of this method of preparation, 3 distinct types of globin are obtained: (a) "native globin," (b) denatured globin, and (c) "paraglobin."

In the purification process employed paraglobin was eliminated, leaving essentially a soluble globin. This material upon recombination with alkaline hematin has given the characteristic band of methemoglobin. It must be remembered that even small amounts of native globin would give the hemoglobin band so that this method of identifying globin is not satisfactory. This was substantiated by Gralen.<sup>9</sup> Stability studies indicated that this globin underwent chemical changes when kept either as a dried powder or as an aqueous solution.

We have found that this globin was toxic to rabbits. Electrophoretic studies indicated that this globin consisted of 2 portions: 40% of a slow component and 60% of a fast component.

*General Properties of "Modified Globin" so far Determined.* As yet, not all the properties of "modified globin" have been fully investigated. The following general attributes are listed at this time: (1) It is soluble in water at pH 7.4 to give at least a 25% solution. (2) It possesses a minimum solubility at about pH 6.5. (3) The viscosity is appreciably lower than that of citrated plasma. (4) The molecular weight of 85% or more of the modified globin as determined by ultracentrifugal studies by Cohn and Oncley<sup>6</sup> is around 34,000. This percentage varies to a certain extent with the process of modification. (5) Preliminary studies indicate that the molecule is quite symmetrical. (6) The approximate yield is about 250 gm. for each 1000 cc. of packed erythrocytes. (7) Preliminary observations indicate that solutions in 0.85% saline solution are stable under ordinary conditions of preservation. (8) Solutions are miscible in all proportions without precipitation, clumping or hemolysis with citrated human plasma and blood. (9) Solutions in saline do not increase the rate of sedimentation of erythrocytes when added either *in vitro* or *in vivo* to whole blood. (10) The intravenous injection of sufficiently large quantities of "modified globin" in normal or hypoproteinemic humans produces an hemodilution lasting, in the majority of cases, 24 to 120 hours.

*Toxicity and Antigenic Properties.* Globin solutions injected intravenously in rabbits and intraperitoneally in guinea-pigs and mice have been found to be non-toxic. Repeated intravenous administrations of globin to rabbits over a period of several months have not given rise to reactions nor to signs of antibodies formation as determined by precipitin tests. Johnson and Bradley<sup>13</sup> had likewise found that a human globin was non-antigenic when injected into rabbits, although globin similarly prepared from other animal species proved to be antigenic. Weekly injections of globin subcutaneously to small guinea-pigs for periods up to 8 weeks have shown no anaphylactogenic properties. In these experiments the globin was *not* alum precipitated.

In the human, skin tests in over 100 patients belonging to all blood groups have shown no positive reactions. Patients receiving large doses of globin intravenously over long periods of time have shown no late untowards reactions.

So far, a total of 210 intravenous injections of globin have been administered to 108 humans. The total amount of globin thus administered is 3734 gm. The largest single dose has been 57 gm., the largest amount to 1 patient in 24 hours 60 gm. One patient received

92 gm. in 36 hours. The largest total amount administered to any one patient has been 192 gm.

Several patients have received repeated injections of globin over long periods of time. All these patients showed no reaction to any injection and repeated skin tests yielded a negative result.

The concentration of the globin administered intravenously to humans has varied from 1.8 to 6.8%.

A few pyrogenic reactions which occurred in the beginning were readily eliminated by instituting the usual biologic controls. The use of modified globin prepared by the standard method has given rise to no severe reactions nor any delayed untowards effect.

Solutions of some globins have shown in some persons a pressor effect and solutions of other globins a vasomotor effect. None of these reactions could be considered as severe; but they can be largely eliminated by proper technique in the preparation of the globin and subsequent purification.

Globins containing large molecular aggregates, soluble in alkaline pH range only, have given rise, when injected intravenously in experimental animals, to embolic lesions, with immediate death or severe organic damage. In the method of preparation followed for modified globin used in humans, the material unstable at pH around 7.4 has been carefully eliminated.

*Use of Modified Globin in the Treatment of Secondary Shock.* Up to the present time 15 patients suffering from secondary shock have been treated with globin solutions. Two have received inadequate amounts of globin and 13 have received sufficient amounts of globin to combat the shock. All of these patients are considered as having responded satisfactorily to the treatment.

These patients may be divided as follows:

1. Shock as a result of hemorrhage and tissue destruction from bullet wound	2
2. First, second and third degree burns involving one-half of body surface	1
3. Shock from hemorrhage from stab wounds	2
4. Hemothorax and cerebral hemorrhage as a result of automobile accident	1
5. Postoperative shock	9

They will be reported separately in detail.

**Comments.** The expression "plasma substitute" used in this paper is not to be construed as meaning that globin solutions can replace plasma in all instances. At best, "modified globin" solutions can be expected to replace plasma insofar as colloidal osmotic properties are concerned.

It is estimated that every year nearly  $1\frac{1}{2}$  billion cc. of packed red cells may be made available from the preparation of plasma for the Armed Forces and for the civilian population. By a relatively simple process, this hemoglobin can be transformed into a "modified globin" at a fraction of the cost of plasma production.

From the amount of red cells mentioned above 375,000 kg. of globin can be prepared, with an osmotic power about twice as great as an equivalent amount of plasma proteins, that is, an osmotic equivalent of about  $12\frac{1}{2}$  million liters of citrated plasma. In other words, from a blood donation it is possible to obtain about 250 cc. of plasma (about



17 gm. of plasma proteins) and about 24 gm. of globin. This globin is equivalent in osmotic power to about 600 cc. of plasma. Thus from a single 500 cc. donation of blood it is possible to obtain the osmotic equivalent of about 4 donations.

As yet, the properties of this modified globin have not been fully investigated. It has been ascertained that this material is: (1) safe; (2) capable of replacing lost blood volume in cases of severe secondary shock.

These results justify a full-scale investigation to determine more completely the physicochemical, physiologic and pharmacologic properties of this modified globin.

**Conclusions.** A "modified globin" can be prepared from human erythrocytes left over from plasma preparation. This globin is safe and has been satisfactorily used as a plasma substitute to restore lost blood volume in human patients suffering from secondary shock.

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## HEMOPHILIA-LIKE DISEASE IN THE FEMALE

## WITH A NOTE ON THE CLOTTING TIME OF THE RECALCIFIED PLASMA

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By definition hemophilia is a bleeding disease manifesting itself early in life, occurring only in the male but being inherited through the female. The question whether the characteristic active defect of hemophilia can occur in women has not been satisfactorily answered. A number of cases have been reported which closely approximate the clinical picture of hemophilia and have the characteristic delay in coagulation time without other demonstrable hemostatic defects. Until recently, however, the diagnosis of hemophilia has been uncertain and subject to serious error; consequently all cases which have not conformed to the classical definition must be viewed with reservation. It is felt that the following case may shed further light on the group of hemophilia-like diseases occurring in the female.

**Case History.** Mrs. H. B., age 30, housewife, was first seen in February 1943 in consultation with Dr. P. Curren. Her father had died at the age of 57 with carcinoma of the rectum and her mother had died at 33 with pneumonia. Three brothers and 1 sister were living and well and no siblings had died. There was no known instance in the family for 3 generations of abnormal tendency to bleed or to bruise easily. The past medical history was entirely negative except for repeated attacks of tonsillitis before the age of 10, otitis media at the age of 4 and a small duodenal ulcer at the age of 19 which healed promptly with dietary control. She had had 3 normal pregnancies, all of which had been terminated by Cæsarean section; the last one in December 1941 without unusual bleeding. Menstrual flow since the last pregnancy had been somewhat greater than previously but had never required more than 5 to 6 pads daily for 3 to 5 days. In April 1942 there had been a rash around the waist which was thought to be "shingles." In May 1942 she noted for the first time a sudden sharp unexplained pain deep in the left calf muscles which was followed with moderate swelling, pain and, in 36 to 48 hours, extensive ecchymosis. This experience was repeated in the arm in a few days and subsequently in multiple areas, many of which showed only moderate swelling and ecchymosis. In no instance was trauma responsible for the sudden hemorrhage—in fact, the patient recalled a severe fall on her knee without bruising. She had 2 severe episodes of hematuria—the first attack lasted 3 weeks while the latter subsided in 4 days but was very severe and was accompanied by pain over both renal areas. The characteristic deep muscular and subcutaneous hemorrhages continued until in October 1942, when the gums bled for a short period and the deep hemorrhages seemed to increase in size and frequency to the time of observation. At that time (February 1943) hemorrhages were of sufficient extent to incapacitate the patient for a few days and to cause very severe pain.

Physical examination was entirely negative except for marked swelling and

tenderness of the left forearm from the wrist to the elbow and variably sized ecchymotic areas over the other extremities. Laboratory findings were:

Hemoglobin	13 gm.
R.B.C.	3,970,000 (mild normochromic anemia)
W.B.C.	8650 (normal differential count)
Platelets	316,000 (normal)
Sedimentation rate	30 mm. in 1 hour
Plasma ascorbic acid	0.5 mg.
Tourniquet test	Moderately positive (25 petechiæ in 2.5 cm. circle)
Coagulation time (Lee-White method)	17 minutes (delayed)
Coagulation time of recalcified plasma	5 minutes (normal)
Clot retraction complete in	40 minutes (normal)
Bleeding time	2 minutes (normal)
Prothrombin concentration	100%

She was given large amounts of fruit juices, cevitamic acid and subsequently hesperidin without appreciable effect on the tourniquet test. The muscular and subcutaneous hemorrhages continued with variable frequency. On March 4, 1943 hemorrhagic study showed:

Clotting time (Lee-White method)	19 minutes
Clotting time of recalcified plasma:	
After high centrifugation	6 minutes 15 seconds
After low centrifugation	5 minutes 30 seconds
Prothrombin concentration	100%
Platelets	260,000 (normal)
Tourniquet test	2+
Hemoglobin	12.5 gm.
R.B.C.	3,840,000
W.B.C.	6450

A period of apparent improvement followed and on April 21, 1943 the tourniquet test was normal and the blood count was within normal limits. Suddenly during the night of April 25 spontaneous hemorrhage appeared in the base of the tongue and the mucosa of the pharynx causing difficulty in breathing and swallowing. Hemorrhagic study on hospital admission showed:

Coagulation time (Lee-White)	21 minutes
Bleeding time	2½ to 4½ minutes (normal)
Clot retraction	95 minutes (normal)
Prothrombin	90 per cent
Platelets	290,000

The clinical course seemed satisfactory for 36 hours when complete respiratory obstruction occurred very suddenly. Tracheotomy was done immediately but in spite of oxygen and artificial respiration, the patient failed to respond.

The *autopsy* findings were completely negative except for the extensive hemorrhagic infiltration of the sublingual, submaxillary and laryngeal areas and slight tubular degeneration of the kidneys.

**Discussion.** It is obvious that this case resembles hemophilia both clinically and in the laboratory findings. The bleeding into the muscles, intermittent hematuria and the final hemorrhage into the base of the tongue observed in this case are common forms of bleeding in hemophilia.

As in hemophilia, the patient's bleeding time, clot retraction time, prothrombin concentration and platelet count were normal, whereas the coagulation time was distinctly delayed. There were, however, striking differences between the hemorrhagic diathesis of our patient and true hemophilia. The latter disease appears early in childhood, occurs

exceedingly infrequently if ever spontaneously in adults, and has the well-known characteristic hereditary pattern.

The laboratory findings are similar in both this hemophilia-like condition and the true hereditary disease except for one test—the clotting time of recalcified plasma. Oxalated hemophilic plasma subjected to high centrifugation clots significantly slower on recalcification than that obtained by spontaneous sedimentation or slow centrifugation. In marked contrast the plasma of this patient failed to show this striking difference due to centrifugation. The significance of this test is not yet known, but one of us has observed that the test has been consistently positive in a small series of hemophilia cases<sup>4</sup> and that it was negative in one other atypical or hemophilia-like condition.

The relationship of this diathesis to the other hemorrhagic diseases presents an interesting and important problem. According to the commonly accepted classification, the true bleeding diseases can be divided into two primary groups: one in which the hemostatic defect is vascular, the other in which a disturbance of the coagulation mechanism occurs. In the first class the coagulation is normal while in the second class it is delayed or absent. Coagulation of the blood depends on 3 factors: fibrinogen, prothrombin and thromboplastin; therefore, diminution or absence of any one of these agents in the blood causes a retardation of clotting. It is now well recognized that fibrinogen and prothrombin are not diminished in hemophilia, but with the less critical diagnostic methods of the past it is probable that cases of hypofibrinogenemia were erroneously called hemophilia. Hypoprothrombinemia, especially the idiopathic type, likewise has been mistaken for hemophilia. The case of Rhoads and Fitz-Hugh<sup>5</sup> was regarded as hemophilia for 9 years before the low prothrombin of the blood was discovered. Since the clinical picture of idiopathic hypoprothrombinemia closely resembles that of hemophilia, one must conclude that at least some of the cases of atypical hemophilia recorded in the literature were in reality hypoprothrombinemias. Unfortunately all these cases are valueless unless restudied with the newer methods, for it is impossible to arrive at an unequivocal diagnosis on the basis of the data consisting of the clinical history and the coagulation time.

It is evident that hemorrhagic conditions exist which, like hemophilia, lack available thromboplastin, or to state it in an entirely non-controversial manner, in which the prothrombin is activated too slowly to meet the hemostatic demands. In this group can be included the newly discovered hemorrhagic disease of swine.<sup>3</sup> Curiously this disease is transmitted by and occurs in both sexes. Except for this it closely resembles human hemophilia. The coagulation time of recalcified oxalated plasma is influenced markedly by centrifugation just as in true hemophilia.

Our case demonstrates that a hemophilic-like diathesis which is not hemophilia can occur in women. In 1938 Joules and Macfarlane<sup>1</sup> described a similar case of a woman aged 56 who, following an extraction of a tooth, developed a hemorrhagic diathesis—hematuria, rectal bleeding, hemorrhage into tissues such as her tongue and joints.

The family history was entirely negative in regard to hemorrhagic diseases. Interestingly, the blood when mixed with Russell viper venom (a thromboplastic-like agent) clotted nearly as fast as normal blood, thus behaving similar to hemophilic blood. The clotting times (with venom) of their patient, of a normal and of a hemophilic subject were 31, 17 and 23 seconds respectively. The Lee-White coagulation time of the patient ranged from 43 to 67 minutes. Obviously the defect in coagulation was in the availability of thromboplastin, and therefore this case is identical or closely related to ours.

Recently Dr. Albert Loveman<sup>2</sup> informed us of a case closely simulating the one we have described. His patient, a woman aged 33, developed a hemorrhagic diathesis a year after the birth of a child. The hemorrhages were mostly superficial—subcutaneous rather than intramuscular—with spells of epistaxis and one attack of hematuria. The prothrombin was 88% of normal and the Lee-White coagulation test 1 hour and 50 minutes. The family history was negative.

These 3 cases appear to be essentially identical. In each the hemorrhagic condition appeared in an adult female who had had no previous attacks of abnormal bleeding nor any history of hemorrhage in the family. The clinical picture and the type of bleeding simulates hemophilia, and is almost certainly due to the prolonged coagulation time of the blood. The diathesis can be equally as serious as hemophilia and may terminate fatally as illustrated by our patient. In the case of Dr. Loveman as well as in ours, the hemorrhagic condition began several months after the birth of a child. Whether this was merely incidental is difficult to say. Significantly in both patients menstruation was normal and unaccompanied by excessive bleeding in spite of a prolonged coagulation time which seems to indicate that the hemostatic control of menstrual bleeding is not dependent upon the coagulation mechanism.

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF HEMOPHILIA AND HEMOPHILIA-LIKE DISEASES

	Human hemophilia	Swine hemophilia	Hemophilia-like disease in women
Heredity . . . . .	Recessive sex-linked	Simple recessive	
Sex appears in . . . . .	Male	Male and female	Female*
Transmission by . . . . .	Female	Male and female	
Time of onset . . . . .	Infancy	Early	Adult life
Bleeding: Type . . . . .	Deep	Deep	Deep
Cause . . . . .	Traumatic	Traumatic	Spontaneous
Coagulation . . . . .	Delayed	Delayed	Delayed
Clotting time test of recalcified plasma . . . . .	Positive	Positive	Negative

It is interesting to speculate as to the rôle of the vascular dysfunction in the bleeding of our patient. The tourniquet test was positive on

\* The authors have been informed by Dr. B. E. Hall that he has studied a male patient at the Mayo Clinic who presented a clinical picture similar to the case described in this paper. The patient had a negative family history concerning bleeding diseases, and he showed no hemorrhagic tendency until at the age of 52 years. He had rectal bleeding and several ecchymoses. There was also marked swelling and limitation of motion of the left knee. Laboratory findings were normal except for a delay of the coagulation time of the blood (40, 36 and 55 minutes).

several occasions and the hemorrhages occurred without any demonstrable preceding trauma. These findings are characteristically present in purpura and not in hemophilia. It would seem justifiable to regard the vascular changes in this instance as coincidental rather than as secondary or related to the coagulation defect and of clinical importance only in relation to the spontaneous nature of the bleeding. The coagulation defect appears to be the primary factor and it seems appropriate that the term "hemophiloid" be considered in describing such a diathesis as one of us has previously suggested.<sup>5</sup>

The principal differences between this clinical entity, true hemophilia, and the hemophilia-like disease of swine are summarized in Table 1.

Treatment is as unsatisfactory as in hemophilia. Transfusion must be looked upon as a makeshift therapy, but as the best so far known. In view of the fact that after numerous studies divergent theories are still held concerning the fundamental defect in hemophilia, it seems unwise to attempt an explanation of the coagulation disturbance in this new entity. Only as theoretical studies advance knowledge concerning the fundamentals of coagulation can a solution of hemophilia and allied conditions be expected.

**Summary.** A study is presented of a female patient with a hemorrhagic disease that closely simulates hemophilia. The disease is discussed and its similarity to and its differences from true hemophilia are considered.

The diagnostic value of the clotting time test of recalcified plasma is pointed out.

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### CARDIAC HYPERTROPHY AND EXTRAMEDULLARY ERYTHROPOIESIS IN NEWBORN INFANTS OF PREDIABETIC MOTHERS

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RECENT studies have shown that striking changes frequently occur in many of the tissues of infants born to diabetic mothers. In addition to the increased body weight and hyperplasia of the islands of Langerhans, which have been recognized for many years, it has been demonstrated that these infants sometimes have at birth cardiac hypertrophy and extramedullary erythropoiesis,<sup>8</sup> adrenal hyperplasia,<sup>7</sup> an increased

eosinophilia of the anterior hypophysis<sup>1,4,9</sup> and hyperplasia of the genital organs in the female.<sup>2,10</sup> In the course of their study of infants born to diabetic mothers, Miller and Wilson observed that many of the above changes were present in 2 infants born before signs or symptoms of diabetes appeared in their mothers.<sup>8</sup> Similar observations were made in 2 other infants by Miller, Johnson and Durlacher<sup>7</sup> and in a fifth infant by Miller, Hurwitz and Kuder.<sup>6</sup> The diagnosis of this syndrome in infants born to mothers who have not yet developed diabetes is of importance to the clinician not only in directing the care of the infant in the neonatal period but also in anticipating the onset of diabetes in the mother. In order to make it possible for more infants with this symptom to be recognized, the relevant clinical and autopsy findings in the 5 infants mentioned above and the case histories of 2 other infants, who survived, are brought together in this report.

TABLE 1.—SIGNIFICANT CLINICAL DATA ON PREGNANCIES OF 7 MOTHERS WHO LATER DEVELOPED DIABETES

Case	Present pregnancy				Diabetes				Kahn	Rh
	Gravida	Age	Glycosuria	Blood sugar (mg. %) (fasting)	Time of onset after pres. preg.	Character of onset	Regulated by	Period of diabetic follow-up		
1 <sup>1</sup>	2	22	0, day before and day of delivery	68, day of del.	4 mos.	Gradual	Insulin	7 mos.	Neg.	
2 <sup>1</sup>	8	43	0, 3 and 8 days postpartum	75, day of del.	1½ yrs.	Gradual	Diet	6 mos.	Neg.	
3 <sup>2</sup>	2	24	0, 5 months antepartum	.....	9 mos.	Gradual	Insulin	15 mos.	Neg.	Neg.
4 <sup>5</sup>	5	38	0 to 4+, for 2 mos. antepartum	116, 96 and 117, last trimester	6 mos.	Gradual	Insulin	9 mos.	Neg.	Pos.
5 <sup>2</sup>	6	30	0, postpartum	.....	5 yrs.	Gradual	Diet	3 mos.	Neg.	
6 <sup>2</sup>	12	38	0, 1 day postpartum	.....	2 yrs.	Gradual	Diet	3 yrs.	Neg.	Pos.
7 <sup>2</sup>	4	36	0, 4 mos., 1 mo. and 9 days antepartum	....	2 days	Sudden with acidosis	Insulin	9 yrs.	Neg.	

\* See Case Reports 1 and 2.

The significant clinical facts on the 7 mothers are summarized in Table 1. They were multiparas whose ages ranged from 22 to 43 years at the time of the births of the infants reported in this study. The Kahn tests on the mothers' bloods were negative. Rh determinations were made in 3 mothers: 2 were Rh positive (Cases 4 and 6) and 1 was Rh negative (Case 3). No evidence of glycosuria was found in any of the mothers except 1 (Case 4), and in this instance reducing substances in the urine were found on several occasions in the last 2 months of pregnancy. However, the fasting blood sugar concentrations in this mother were not over 117 mg. per 100 cc. on 3 separate occasions during the period glycosuria was present. Two other mothers (Cases 1 and 2) had normal fasting blood sugar concentrations on the day of delivery. None of the 7 mothers had any symptoms of diabetes before or during the pregnancies under discussion. Signs and

symptoms of diabetes developed in the mothers from 2 days to 5 years following the births of these 7 infants. In all but 1 mother (Case 7) the onset of diabetes was gradual. In Case 7 there was a sudden onset of diabetic acidosis 2 days postpartum, associated with a respiratory infection and pyelitis. During the time they were under observation for their diabetes 4 of the mothers required insulin (Cases 1, 3, 4 and 7), while in the remaining mothers the diabetes was regulated solely by diet.

TABLE 2.—SIGNIFICANT AUTOPSY FINDINGS IN 5 INFANTS WHOSE MOTHERS LATER DEVELOPED DIABETES

Case*	Day of death	Birth wt. (kg.)	Heart wt. (gm.)	Extramedullary erythropoiesis	Hyperplasia islands Langerhans	Adrenals wt. (gm.)	Anterior hypophysis
1	Stillborn	5.9	29	Liver			
2	Stillborn	5.5	65		++		
3	2	4.4	50	Liver, spleen heart	++++	17	Eosinophilia increased
4	3	2.6	Large by Roentgen ray	Liver			
5	3	4.1	36	Liver and stomach	...	14	

\* Case numbers in this table correspond to case numbers in Table 1. Cases 6 and 7 of Table 1 survived.

The postmortem findings on the 5 infants who died are summarized in Table 2. The data on several of the infants are incomplete because records of the examination of some of the viscera were omitted from the autopsy protocols. Cardiac hypertrophy, as judged by the data on normal heart weight of newborn infants compiled by Miller,<sup>5</sup> was marked in Cases 2, 3 and 5. The heart was not weighed in Case 4, but it was found to be enlarged on Roentgen examination before death and the muscle fibers were described as hypertrophied in the autopsy protocol. There was an excessive amount of erythropoietic tissue in the livers of the 4 infants examined for this change (Cases 1, 3, 4 and 5), and additional evidence of abnormal erythropoiesis was found in the spleen and heart of Case 3 and in the stomach of Case 5. Hyperplasia of the islands of Langerhans was observed in Cases 2 and 3, the only 2 infants examined for this change. Assuming that 10 gm. is the upper limit of normal for the combined weight of the adrenals of the newborn, it can be stated that the suprarenals in Cases 3 and 5 were hyperplastic. Gross hemorrhages into the adrenals were not recorded in either infant. An increase in the eosinophil elements of the anterior hypophysis was noted in Case 3. It is of interest to find in Case 3 all of the visceral changes—cardiac hypertrophy, extramedullary erythropoiesis, hyperplasia of the islands of Langerhans, adrenal hyperplasia and an increased eosinophilia of the anterior hypophysis.

The following case reports are on the 2 infants who survived, Cases 6 and 7 of Table I.

**Case Reports.** CASE 1. New Haven Hosp. Unit A, 91722. The mother of this infant was 38 years old and weighed 200 pounds just before this pregnancy. The Kahn test on her blood was negative. Her blood was Rh positive. There were 12 previous pregnancies, 11 of which had resulted in living children and the 12th in a spontaneous abortion. One of the 11 children was a cretin. The present pregnancy was uncomplicated except for headaches



and blurring of vision. Her blood pressures on several occasions were found to be normal, although she had been told that she had a high blood pressure in another hospital when the baby previous to this was born, and although she had been found to have blood pressures of 175/130 and 155/100 in our

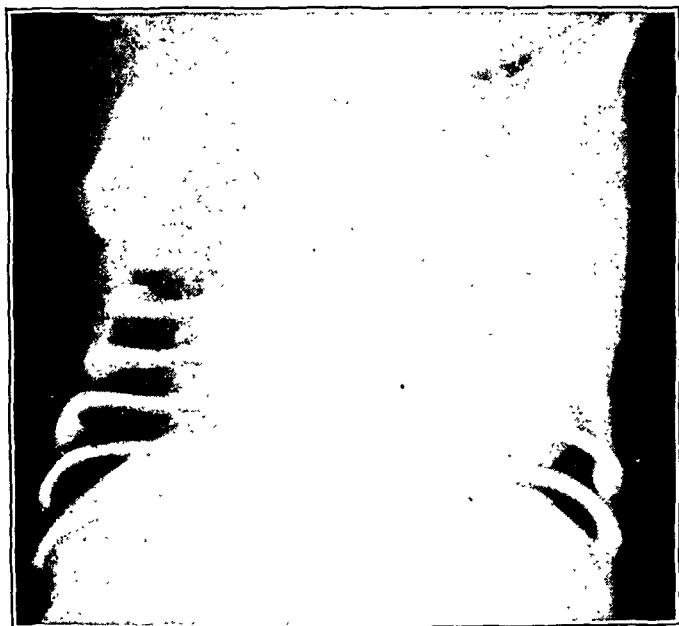


FIG. 1.—Case 1. Age, 1 day. Transverse diameter of heart, 8.1 cm. Transverse diameter of thorax, 11.2 cm. Cardio-thoracic ratio, 72.



FIG. 2.—Case 1. Age, 5 days. Transverse diameter of heart, 7.1 cm. Transverse diameter of thorax, 10.5 cm. Cardio-thoracic ratio, 68.

Medical Clinic 1 year prior to the present pregnancy. The basis for the hypertension was not established. The urine was negative. Throughout the present pregnancy she was so obese that the fetal parts could not be made out. Labor started spontaneously and the baby was delivered 5 hours later without

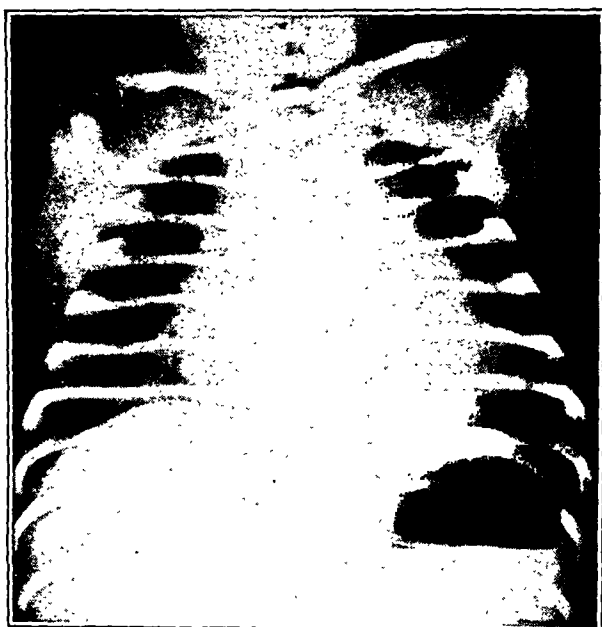


FIG. 3.—Case 1. Age, 7 days. Transverse diameter of heart, 7.1 cm. Transverse diameter of thorax, 10.9 cm. Cardio-thoracic ratio, 65.

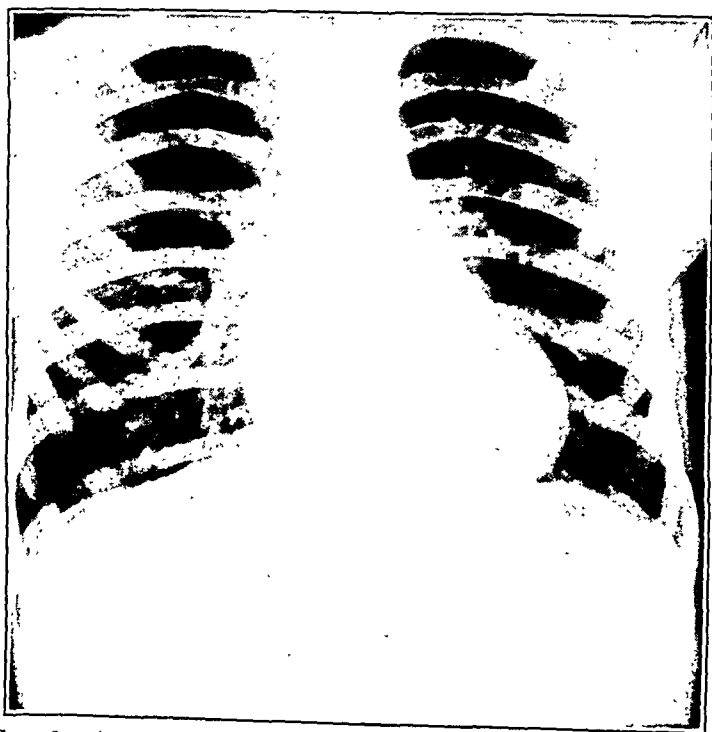


FIG. 4.—Case 1. Age, 5 years. Transverse diameter of heart, 9.4 cm. Transverse diameter of thorax, 19 cm. Cardio-thoracic ratio, 49.

difficulty and without instruments. The baby was a male weighing 4700 gm. The cyanosis which was localized to the head at birth became generalized and marked 2 hours later. He was put in an oxygen tent for the next 48 hours and the cyanosis improved remarkably. Physical examination at birth was not notable except for the presence of a systolic murmur, which disappeared 3 days later, not to be heard again. Roentgen examinations of the heart were made on the 1st day of life and on several occasions thereafter, at a target film distance of 6 feet. The heart remained enlarged during the first 7 days of life as determined by the Roentgen studies (Figs. 1, 2, 3). No further Roentgen ray examinations were made until he was 5 years old, at which time his heart was normal in size and shape (Fig. 4). Cardiac enlargement could not be made out by clinical examination. An ECG done on the 2nd day of life showed the T waves to be diphasic in Lead 1 and the S-T segment to have a peculiar upward convexity in this same lead. Except for S-A tachycardia and right axis deviation, the ECG was not otherwise abnormal. Blood counts were as follows:

Day of life	R.B.C. (millions per c.mm.)	Hg. (gm.%)	W.B.C. (thousands per c.mm.)	Normoblasts (thousands per c.mm.)
1 . . . . .	6.8	18.0	18.3	7.4
2 . . . . .	6.2	18.0	17.1	3.2
4 . . . . .	6.8	18.0	16.0	1.6
5 . . . . .	5.5	18.0	13.0	0.1
6 . . . . .	5.5	17.5		
9 . . . . .	6.2	18.0	12.5	0.0

His course in the hospital was uneventful after the 3rd day of life. He was seen in the follow-up clinic on several occasions during the next 5 years. At 5 he appeared to be a boy of normal intelligence. He weighed 40½ pounds and was 41½ inches in height. Examination of his heart was negative.

Tests for reducing substances in the mother's urine were made routinely in this hospital 2 years and 1 year before the birth of the patient; they were both negative. Similar tests on the mother's urine were found to be negative at the time of his birth and again 18 months later when the mother was admitted to this hospital with fever and abdominal pain of undetermined origin. Six months after the latter admission and 2 years following the birth of the patient, the mother was seen in the Medical Clinic because of pruritus vulvæ and excessive thirst. Examination of her urine showed 4+ reduction of Benedict's solution and a negative acetone test. Her diabetes was regulated solely by means of diet during the next 3 years. Pruritus vulvæ, polydipsia, polyuria and loss of weight continued to be present off and on. She was admitted to another hospital for a check-up of her diabetes 2½ years after the birth of the patient.\* There was sugar in the urine and 2 fasting blood sugar determinations were 195 and 145 mg. per 100 cc. at the time of this admission. Her urine became free of sugar when she was put on a diet.

CASE 2. Boston Lying-In Hosp. Unit, 9994.† The mother was 36 years old. The Kahn test on her blood was negative. There were 3 previous pregnancies. The first infant was born at home and died on the 15th day of life with "meningitis." The second infant also was born at home and died at birth. The third pregnancy resulted in a macerated fetus. The fourth and present pregnancy was uneventful except for the presence of hydramnios. Her urine was routinely tested for sugar 3 times during this pregnancy: 4 months, 1 month, and 9 days before delivery. The tests were all negative. In view of the 2 neonatal deaths and 1 stillbirth that had occurred in her previous pregnancies, it was decided to terminate the present pregnancy by Cesarean section. This was accomplished without difficulty at term before labor had started, and a male infant weighing 5100 gm. was born. On the

\* I am indebted to Dr. A. Capeceaturo of New Haven for permission to report the data obtained on this hospital admission.

† Dr. Frederick C. Irving, Visiting Obstetrician, Boston Lying-In Hospital, kindly gave permission for the publication of the data on this infant and mother.

6th day after birth the infant's temperature was  $103^{\circ}$  and he was noted to be "jittery." The red blood cells were 4.8 million per c.mm. and the hemoglobin was recorded as 90%. No normoblast counts were made. A Roentgen ray of his heart on the 6th day showed that the heart was enlarged, the cardio-thoracic ratio being 60. By the 16th day the cardio-thoracic ratio on the roentgenogram had returned to normal, being 52. The "jitteriness" was present on the 7th day of life but not afterwards. Fever was not present after the 6th day. During the first 5 days of life he lost 13.5% of his birth weight. A systolic murmur was heard over the precordium from the 7th to the 13th day. He was discharged from the hospital at the age of 2 months weighing 6 kg. and in good health. Physical examination at the time of discharge was negative.

Two days after delivery the mother became acutely and suddenly ill. She was found to have fever. An intraabdominal complication of the operative procedure was considered. An upper respiratory infection and pyelitis were diagnosed. Fasting blood sugar concentrations of 182, 167 and 250 mg. per 100 cc. were found on the 2nd, 3rd and 4th days postpartum. A diagnosis of diabetic acidosis was made and she was treated with insulin. Nine, 15 and 24 days postpartum her fasting blood sugar concentrations were 250, 143 and 182 mg. per 100 cc. Her diabetes improved. The insulin dosage was gradually reduced and she was discharged without any insulin. She was followed in the Out-Patient Clinic of the Beth Israel Hospital in Boston and on her last visit, 9 years after the birth of the patient, 8 to 10 units of protamine zinc insulin daily were again advised in order to better regulate her diabetes.\*

**Comment.** The postmortem findings in the infants in Table 2 are similar to those described in infants born to diabetic mothers.<sup>7,8</sup> The clinical findings in the 2 infants who survived (Cases 1 and 2)—the increased birth weight, cardiac hypertrophy and excessive normoblastemia—are in no way different from those described by Miller and Wilson in some infants born to diabetic mothers. Although the findings are the same in the infants regardless of whether or not maternal hyperglycemia has been established, the absence of diabetic symptoms and signs in the mothers makes the diagnosis of the syndrome in the infants of these mothers more difficult.

The difficulty in diagnosis can be partly overcome by anticipating the presence of the syndrome in infants with an excessive birth weight and newborn infants with cardio-respiratory symptoms. Infants with a birth weight of 4500 gm. or more make up only 1% of the population.<sup>3</sup> Since the syndrome has its highest incidence in this birth-weight group, the routine use of Roentgen studies of the heart and normoblast counts can be expected to aid in establishing the diagnosis in a number of these infants. The exact incidence of the syndrome in this birth-weight group has not been established. The routine employment of Roentgen studies and normoblast counts in infants who have cyanotic spells, dyspnea and tachypnea during the neonatal period regardless of their birth weight will increase the number of infants in whom the diagnosis of this syndrome can be made.

Two important facts must be kept in mind in diagnosing this syndrome in living newborn infants: the size of the heart diminishes very rapidly and the normoblasts disappear from the peripheral blood

\* I am indebted to Dr. H. A. Derow, Director, Out-Patient Department, for the information concerning her follow-up visits at the Beth Israel Hospital.

relatively early. Hence, the study of both these conditions should be initiated within the 1st or 2nd day after birth.

The differential diagnosis will include infants with cardiac hypertrophy associated with congenital malformations of the heart or its great vessels. Cardiac hypertrophy associated with malformations would not be expected to return to normal size within the 1st or 2nd month of life as it does in infants born to diabetic mothers or mothers who later develop diabetes.<sup>8</sup> Furthermore, cardiac and respiratory symptoms, when present in the latter group of infants, have not been known to persist beyond the first 10 days of life, while in those with congenital anomalies they frequently persist for weeks and months. Although cardiac murmurs can be heard during the first few days of life in infants with cardiac hypertrophy unassociated with congenital anomalies, they are not known to persist as they so frequently do in infants with congenital heart disease. The possibility that the mother of an infant with a heart that is enlarged as the result of some congenital anomaly might subsequently develop diabetes cannot be excluded. Congenital malformation of the heart among infants born to diabetic mothers has been observed, but it is uncommon.

The differential diagnosis will also include infants with an excessive normoblastemia associated with sepsis, syphilis, premature birth and erythroblastosis fetalis. Serologic tests for syphilis and blood cultures should help to differentiate the first 2 of these. Cardiac hypertrophy has not been described either in newborn infants with syphilis and sepsis or in infants born prematurely. The greatest difficulty will be in differentiating infants with erythroblastosis fetalis from those born to "prediabetic" mothers, since the former not only have a considerable normoblastemia but also cardiac hypertrophy.<sup>7</sup> It has been shown, however, that unless either anemia or jaundice are present the diagnosis of erythroblastosis fetalis must be viewed with considerable doubt.<sup>7</sup> Hence, red blood cell counts in infants with cardiac hypertrophy and normoblastemia will be of the greatest importance in the differential diagnosis. If the infant is stillborn or dies before anemia or jaundice can develop, there is no way yet known of making the differential diagnosis at postmortem between these 2 groups of infants.

The significance of the visceral lesions and their relation to the diabetic syndrome have been discussed in previous papers in detail.<sup>6,7,8</sup> It is sufficient to reiterate here that maternal hyperglycemia can be excluded as a probable cause of the visceral lesions, the oversize of the fetus, and the high fetal and neonatal mortality seen in infants born to diabetic mothers, since all of these changes are in evidence before maternal hyperglycemia can be demonstrated.

**Conclusions.** 1. A newborn infant can exhibit the same clinical and postmortem changes regardless of whether the mother is diabetic during the gestation period or develops symptoms and signs of diabetes mellitus after the delivery.

2. The changes in the infant can include macrosomia, cardiac hypertrophy, hyperplasia of the islands of Langerhans, excessive extramedul-

lary erythropoiesis, adrenal hyperplasia and an increase in the eosinophil elements of the anterior pituitary gland.

3. The birth of an infant with these findings may be the first sign of impending diabetes mellitus in the mother.

4. The differential diagnosis in newborn infants with the above changes is discussed.

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## ACUTE MYOCARDITIS IN INFLUENZA A INFECTIONS

TWO CASES OF NON-BACTERIAL MYOCARDITIS, WITH ISOLATION  
OF VIRUS FROM THE LUNGS

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A PATIENT, who in mid-December, 1942 had a mild illness that might be construed as clinical influenza, became acutely ill early in April, 1943 and died in 6 days. The fatal illness was accompanied by fever, chills, extreme prostration and progressive dyspnea. There was evidence of marked myocardial weakness and diffuse signs appeared in the lung bases before death. Clinically, the findings were interpreted as those of a rapidly progressing primary atypical pneumonia, probably of viral etiology and similar to others which were prevalent at the time. Autopsy revealed a minimum of pathology in the lungs, but the heart showed an extreme degree of acute diffuse myocarditis.

The isolation of a virus from the lungs of this case and its identification as influenza A makes it a very unusual case and prompted this report.

A brief survey of the literature since the discovery of the influenza viruses reveals no instance of acute myocarditis in a human case from which influenza or, indeed, any other virus was isolated and identified. There are, however, a number of clinical and pathologic descriptions of cases with evidence of myocardial damage associated with epidemic influenza. Some of these occurred during the pandemic of 1918 and even earlier, but most of them were observed in smaller outbreaks since that epidemic. They have been recognized chiefly by the symptomatology and by changes in the electrocardiograms. Myocarditis has also been produced experimentally in animals by the injection of a number of different viruses, but the influenza virus is not among them.<sup>41,42</sup> Some of the clinical reports may be summarized briefly.

Circulatory failure was observed with great frequency during and after the pandemic of 1918.<sup>4,13,18,20,23,36</sup> Most writers ascribed this finding and the deaths in such cases to general intoxication from the infection and not to the heart alone. There were many cases in which abnormalities of rate or rhythm and ECG changes suggested cardiac damage especially to the conducting mechanism.<sup>2,3,6,9,14-16,19-23,25-27,-29,33,37,38,40,44,57</sup> Cardiac dilatation has also been observed in infants and children after influenza-like infections.<sup>35</sup> Isolated instances of sudden death during convalescence from influenza associated with dilatation of the right ventricle have been reported.<sup>5,19,46,52</sup> The frequency with which cardiac abnormalities were noted varied considerably. Hyman<sup>21</sup> estimated that cardiac abnormalities complicated influenza in from 5 to 12% of the cases observed in hospitals in London, Berlin, and Boston. Others have felt that they are the most frequent complications of epidemic influenza,<sup>5,12,38</sup> while still others considered them to be quite infrequent,<sup>1,4,32</sup> and many extensive reports on the clinical aspects of influenza make little or no mention of cardiac complications except in relation to the superimposed bacterial infections.

The cardiac disturbances which have been observed—after influenza include bradycardia, extrasystoles, partial and complete heart block, sinus-nodal block, loss of various complexes and T wave changes in the ECG's. Hypotension has been observed frequently, and in many instances the diastolic pressure was found to be low and the pulse pressure increased. The symptoms described as accompanying these findings include weakness, dyspnea, palpitation, anginoid pain, extreme malaise, Stokes-Adams attacks and sudden death. These symptoms are said by some writers to be as common after influenza as they are in mitral stenosis.<sup>5,16</sup> The prognosis, however, is for complete recovery in the postinfluenzal cases in contrast to progression of the symptoms in mitral stenosis. The experience of most clinicians, however, is probably similar to that of MacKenzie,<sup>36</sup> who had never seen a case of influenza in which damage was limited to the heart alone, as in rheumatic fever.

Most of the signs and symptoms mentioned have been ascribed to myocardial weakness or to focal myocarditis. Dilatation of the heart

has also been described. The abnormalities in general are said to be comparable with those seen in various other infections, particularly, scarlet fever and diphtheria, and they are often comparable to the severe myocardial lesions found in the latter. The factor of bacterial infection complicating the influenza in these cases has sometimes,<sup>6,46</sup> but not always, been considered. Such infections may have played an important rôle, as evidenced by the fact that some of the writers have included bacterial endocarditis and purulent pericarditis among the cardiac complications of influenza. The cardiac complications of influenza have been observed infrequently during the acute stage of the disease. More often they have been observed during convalescence. Most writers have noted an almost complete lack of correlation between the severity of the influenza and that of the cardiac findings.

The first case to be presented has the essential characteristics of Fiedler's acute interstitial or acute isolated myocarditis.<sup>10</sup> Most of the reported cases of this condition have been reviewed by Scott and Saphir,<sup>50</sup> Simon and Wolpaw,<sup>51</sup> and Saphir.<sup>47</sup> Two cases resembling the present one and associated with acute respiratory infection have been recently described: one by Hansmann and Schenken<sup>17</sup> and the other by Covey.<sup>7</sup> The first of these is included in Saphir's review, but the latter was reported subsequently and will be discussed later.

A review of the literature on the pathologic changes in the myocardium in influenza reveals considerable differences of opinion. Leichtenstern,<sup>31</sup> writing of the 1889-1890 epidemic, stated that the changes in the heart muscle were due to complicating infections, especially of the lungs, and that such changes were those found in any acute infection, namely, parenchymatous and fatty degeneration. Kuczynski and Wolff,<sup>30</sup> in their review of the 1918 epidemic, found that the myocardium showed no characteristic morphologic changes. Those changes that did occur were only slight and did not exceed those seen in the course of any severe septic illness. Opie<sup>39</sup> stated that the heart muscle showed little evidence of injury, as did Klotz,<sup>28</sup> Winternitz,<sup>55</sup> and Wegelin.<sup>54</sup>

Lucke, Wight, and Kime,<sup>34</sup> reporting on their findings on 126 fatal cases, declared the heart was always more or less affected. However, the myocardial changes they described consisted merely of cloudy swelling and edema of the interstitial tissue.

Saphir,<sup>47</sup> in his comprehensive review of myocarditis, concluded: "Thus, from the reports cited, it seems clear that myocarditis in so-called grip or influenza is exceedingly rare, though myocardial damage which easily may be interpreted as the result of cloudy swelling, may be encountered clinically."

Kirch,<sup>24</sup> reviewing the reports on the 1918 epidemic and recurrences of influenza since then, found that there were degenerative changes in the heart muscle but only very exceptionally an inflammatory process, and this only in the late stages of the disease. He credited Schmorl<sup>49</sup> with being the first to observe this type of myocardial disease.

Schmorl<sup>49</sup> described the pathologic findings in 5 patients who died of



heart failure at varying periods after an attack of influenza. His first case died 10 weeks after a moderately severe attack of influenza uncomplicated by pneumonia. The heart showed an extensive infiltration of round cells and also numerous small scars scattered diffusely throughout the myocardium. Schmorl felt that this lesion represented a late stage of the process found in 3 of his other cases. These 3 showed extensive inflammatory changes affecting the heart muscle accompanied by an interstitial infiltration of plasma cells, round cells and edema. They died suddenly, one 4 weeks and another 5 weeks after the initial illness. The duration of the disease in the 3rd case was not known. The 5th case suffered such severe cardiac damage from an attack of severe influenza and pneumonia that he was unable to return to active duty with the army. The patient died suddenly. At autopsy, his heart was enlarged and microscopically showed numerous acellular scars which, in Schmorl's opinion, were the result of the inflammatory lesions which were similar to those seen in the preceding 3 cases. In summarizing his findings, Schmorl stated that he had never seen such widespread and extensive myocardial damage in any other infectious disease.

Roulet<sup>46</sup> reported 2 patients who died suddenly 2 weeks and 3 weeks respectively following influenza. The myocardium of the 1st case showed extensive acute damage to the muscle fibers associated with an interstitial cellular infiltration. The myocardium of the 2nd case showed much fewer acute lesions, but there were foci where the muscle fibers had disappeared with apparent increase in connective tissue in such areas. Both cases were complicated by streptococcus sepsis, 1 a purulent meningitis, the other a pneumonia with empyema. A streptococcus was cultured from the spleen in both cases and from the meninges in the 1st case. Roulet mentions the similarity of the lesions of the heart in these 2 cases to those seen in streptococcus infections, and states that the rôle of mixed infections is probably much more important in causing damage to the heart than the etiologic agent of influenza. In the introduction to his paper, Roulet mentions the rarity of interstitial infiltrations of the myocardium in the 1918 epidemic. He cited Fahr as having seen it once in 246 autopsies, Glaser and Fritzsche once in 350 and Koupmann 7 times in 244 autopsies. The degree of such infiltrations was directly proportional to the severity of the general septic condition of the patients.

Covey,<sup>7</sup> in discussing so-called Fiedler's myocarditis, described a patient who died suddenly 14 days after a "cold." At autopsy, the heart was enlarged and microscopically showed extensive and severe disease of the myocardium, the lesions apparently being of different ages. Covey felt that the type of histologic changes in the lungs and spinal cord favored a viral etiology. He states that in 14 cases of Fiedler's myocarditis where a history of a preceding infection was established, 6 were either influenza or acute upper respiratory infections. He makes no mention in his case report of bacteriologic or virus studies.

**Case Reports.** CASE 1.\* The patient was a 34 year old white woman who, except for recurrent alopecia areata for 10 to 15 years and a mild anemia that was controlled by ferrous sulfate, was in good health until the middle of December, 1942. At that time she had a mild attack of what was called bronchitis or "flu." This attack began a few days after her husband became ill with what was called "virus pneumonia." Serum obtained from the husband after his attack fixed complement with influenza A in a dilution of 1:64, but the patient's serum was not tested. Following this illness, the patient continued to have cough and fatigue. Examinations by her physician during this period revealed no abnormalities of the heart, lungs or blood. She was again seen on February 26, 1943 because the cough and fatigue continued. At that time, the fourth of a series of roentgenograms of the chest revealed no abnormalities and fluoroscopy showed normal heart and lungs.

On the evening of April 4, 1943, the patient noted that she was unusually tired, and on the following morning she had general malaise and some increase in her cough. On April 6, she had chilly sensations, and that evening her temperature rose to 103.4° F. Her lungs at that time were clear. She was put to bed and given aspirin after which she had drenching sweats and a drop in temperature.

On April 9, her condition became much worse. Her temperature was 102.6° F., the pulse was 124 and regular but feeble and thready in character and the blood pressure was 125/78. There was slight dullness and increased whispered voice and tactile fremitus at the right lung base posteriorly. Many moist râles were heard over this area and a few transient râles were heard at the left base. No cardiac enlargement was made out, but the heart sounds, though audible, were faint and distant. The blood counts showed 4 million erythrocytes and 15,000 leukocytes (70% neutrophils). The urine showed 2+ albumin and 2 to 3 W.B.C. The patient raised no sputum, but culture of the throat yielded mostly *Neisseria catarrhalis* and a few colonies of coagulase positive *S. aureus*. The patient was thought to have pneumonia and was given sulfadiazine, 4 gm. initially and then 1 gm. every 4 hours. (She took a total of 8 or 9 gm.)

Late that evening the patient complained of substernal soreness and tightness. She appeared anxious and distressed. The heart sounds were more distant. The pulse was 132 and irregular, due to extrasystole. There was no cardiac enlargement, no cyanosis and no distention of the neck veins. On the morning of April 10, her condition was about the same. The temperature dropped, but the pulse remained rapid and was apparently regular. The signs in the right lung had extended up to the level of the scapula. In the afternoon, she became much worse. Her pulse became weaker and she developed pallor, cold clammy skin, marked anxiety, rapid shallow respiration and a sense of suffocation and substernal constriction.

She was then taken to the Peter Bent Brigham Hospital late in the afternoon. On arrival there, she was extremely ill. Her temperature was 102.2° F, the pulse could not be felt at the wrist and the blood pressure was 80/70 (?). She was restless, anxious, breathing rapidly, and moaning. Her extremities were cold and clammy. The neck veins were not distended. At the right lung base, there was dullness, bronchial breathing and numerous medium moist râles. The breath sounds at the left base were suppressed; and scattered râles were heard throughout the left lung. The heart did not seem enlarged, but the sounds were very faint and distant. The abdomen was distended but non-tender, and the liver and spleen were not felt. The W.B.C. was 20,000, predominantly neutrophils, and these did not show toxic granulations. Sputum could not be obtained.

The patient was given morphin  $\frac{1}{4}$  gr. before being sent to the hospital. This was repeated shortly after her arrival when oxygen, administration by mask, was started. She was relatively comfortable after this for about 4 hours, but

\* We are indebted to Drs. Lewis Kane and Charles A. Janeway for details of this case, and to Drs. Sidney B. Luria and Orville T. Bailey of the Peter Bent Brigham Hospital, who performed the autopsy.

her condition, otherwise, remained unchanged. A bedside roentgenogram of the chest at that time showed diffuse fine mottling of both lungs with irregular streaky consolidation radiating from the left hilum through most of that lung. There were more localized denser areas near the right cardiac border and at the base of the right upper lobe. There was also a thin layer of fluid discernible along the left axillary border and partly obscuring the costophrenic sulcus. These findings were interpreted as compatible with atypical pneumonia. An ECG showed complete A-V block and extreme slurring of the QRS complexes and was interpreted as indicating an extreme degree of myocardial damage (Fig. 1). The patient failed rapidly and despite the administration of stimulants, she died shortly after midnight.

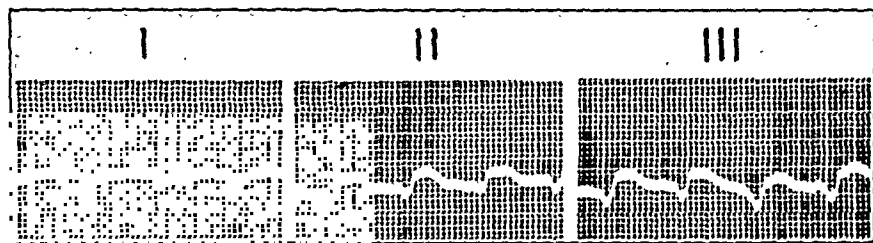


FIG. 1.—Electrocardiogram taken 2 hours before death in Case 1 and showing complete heart block and bizarre ventricular complexes.

AUTOPSY was performed 8 hours after death. Only the pertinent findings are given.

*Peritoneal cavity:* There were 300 cc. of clear yellow fluid. *Pleural cavities:* Right pleural cavity contained 950 cc. of a pale yellow cloudy fluid with some flecks of fibrin, and the left pleural cavity contained 600 cc. of similar fluid. *Pericardial cavity:* There was 1 small hemorrhagic area 1 x 0.5 cm. overlying the edge of the right ventricle. The pericardial cavity contained approximately 40 cc. of clear yellow fluid.

*Heart:* Weight 490 gm. Valve measurements were: tricuspid 10 cm., pulmonary 8, mitral 9, aortic 7. The left ventricle was 2 cm. thick, and the right 0.8 cm. The individual chambers of the heart were slightly dilated. The valves were negative. The myocardium was light pink, being somewhat paler than normal. It had the usual consistence and texture. Coronary arteries were negative.

*Lungs:* Lungs were moderately increased in weight. They were fairly crepitant throughout save posteriorly, especially at the bases where there was less crepitation. On section, a considerable amount of bloody fluid could be expressed from the cut surface. No areas of consolidation were present. The mucosæ of the bronchi were slightly reddened, but were glistening and free from exudate. The blood-vessels were negative.

*Microscopic Examination.* *Heart* (Figs. 2 and 3): The myocardium showed very extensive changes. This was true of the walls of all chambers of the heart. The lesions of the cardiac muscle were evidently of different ages. In the earliest stage, the affected muscle fibers were coarsely granular. These coarse granules represented the cross striations which had become much thicker and fewer in number. The longitudinal fibrils were also granular or had completely disappeared. The nuclei of the muscle fibers were usually no longer recognizable. The involved fibers were infiltrated with a few large mononuclears. At a later stage, the muscle fibers became swollen and hyaline with complete loss of both cross striations and longitudinal fibrils. The fibers stained homogeneously and intensely with phloxine and, after staining with Mallory's phosphotungstic acid hematoxylin, they stained red instead of the blue of normal fibers. The necrotic fibers were invaded by varying numbers of

larger mononuclears. In the oldest lesions the necrotic fibers had been completely removed and were replaced by focal collections of larger mononuclears. The necrotizing process involved a small portion of a fiber or it affected the greater part of a fiber. There was an extensive infiltration of the interstitial



FIG. 2.—Case 1. Myocardium. Necrotic muscle fibers and interstitial infiltration. (Phloxine methylene blue,  $\times 160$ .)

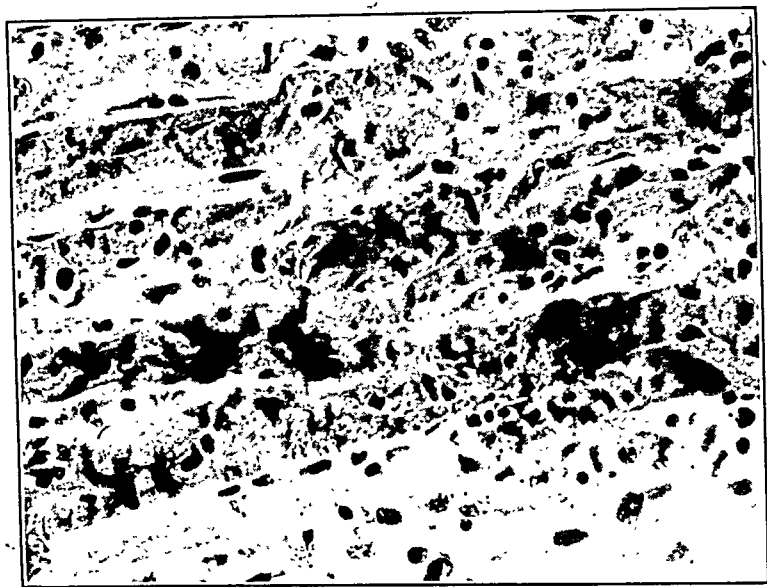


FIG. 3.—Case 1. Myocardium. Necrotic muscle fibers invaded by large mononuclears. (Phloxine methylene blue,  $\times 325$ .)

tissue with lymphocytes, plasma cells, some large mononuclears and occasional eosinophils and mast cells. This infiltration was most marked in the vicinity of the necrotic muscle fibers. The interstitial connective tissue appeared edematous. The blood-vessels were negative except for an occasional small

vein which showed a subendothelial infiltration of a few large mononuclears, lymphocytes and plasma cells.

The epicardium was edematous and was infiltrated with a few large mononuclears, lymphocytes and plasma cells.

The endocardium was infiltrated with numerous cells similar in type to those seen in the interstitial tissue of the myocardium.

*Lungs* (Fig. 4): The lungs showed a considerable degree of congestion. The alveoli contained a variable number of large mononuclear cells, many of which had phagocytosed carbon. Sections from the right lower lobe showed in addition a perivascular infiltration with a few lymphocytes, plasma cells, eosinophils and an occasional mast cell. In the left upper lobe there was one focus of acute inflammation. Here several alveoli contained polymorphonuclear leukocytes, strands of fibrin and some large mononuclears. The walls of these alveoli were infiltrated with polymorphonuclear leukocytes, plasma cells, lymphocytes and large mononuclears. Stains for bacteria failed to reveal any microorganisms in this lesion. Some of the bronchioles showed a slight infiltration of lymphocytes, plasma cells and a rare polymorphonuclear leukocyte in their walls.

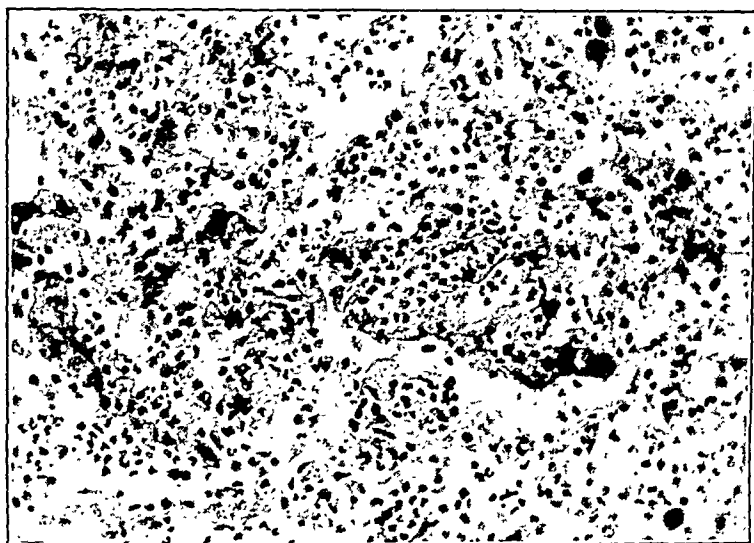


FIG. 4.—Case 1. Lung. Focus of acute inflammation with fibrin and leukocytes in the alveoli. (Phloxine methylene blue,  $\times 160$ .)

*Spleen:* The Malpighian corpuscles contained active histiocytes, some of which had phagocytosed nuclear debris. There were a few stem cells and myelocytes in the pulp. Several veins showed a subendothelial infiltration of a few lymphocytes, plasma cells and a rare mast cell. *Liver:* There were a few areas of necrosis of the liver cells at the centers of the lobules. A considerable number of liver cells showed fatty degeneration and also, in the central portions, hydropic degeneration.

*Kidneys, Adrenals, Bladder, Ovary, Uterus, Aorta, Brain, Pituitary and Choroid Plexus:* Essentially negative.

*Bacteriologic and Chemical Studies.* Cultures of the blood, lungs and serous cavities taken at autopsy were negative. No diphtheria bacilli could be cultured from the nose and throat. Serum, pleural and cisternal fluid obtained at autopsy showed no cold agglutinins and no complement fixing antibodies for the psittacosis group (done by Dr. Karl F. Meyer) or for influenza A (PR8 strain). The total protein of the pleural fluid was 1.86 gm.% and its

non-protein nitrogen was 70.6 mg. per 100 cc. The sulfadiazine levels of the plasma was 7 mg. per 100 cc. free and 10.5 mg. per 100 cc. total and of the pleural fluid 7.9 mg. per 100 cc. free and 10.1 mg. per 100 cc. total.

The findings in this case were considered to be sufficiently rare and important to warrant a further search for evidence of similar cardiac lesions in other cases of influenza. For this purpose, there was available material from the 8 cases of staphylococcal pneumonia which occurred as complications of influenza in the epidemic of 1940-41 and were described by Wollenman and Finland.<sup>56</sup> The evidence suggested that these cases probably began as influenza A infections.<sup>43</sup> Cardiac symptoms had occurred in the so-called chronic cases of this group, and were considered to be secondary to pulmonary fibrosis.<sup>11</sup> In 1 case of this series abscesses were found in the myocardium as part of a staphylococcal septicemia but no other cardiac lesions were found. Autopsies in one other sporadic case and in 4 cases which occurred during the epidemic of 1943-44 were also available. Influenza A was isolated from all but 1 of these 5 cases. Lesions were found in the heart of one of the epidemic cases. A brief report of this case follows.

**CASE 2.** An extremely ill 39 year old Italian iron worker was admitted to the Boston City Hospital January 31, 1944 complaining of breathlessness and hemoptysis of 2 days duration. He was apparently in good health until January 23 when he had a slight "head cold" which was followed by general malaise, apathy, anorexia, and prostration. On January 26, he had several shaking chills followed by feverishness. On January 29, he began to have marked dyspnea and cyanosis accompanying a severe cough which was productive of grossly bloody sputum and which continued to the time of entry. He also had 2 attacks of substernal pain and some vague pains in his legs. The patient denied all previous symptoms of cardiorespiratory illness.

On admission, the patient was markedly cyanotic and dyspneic with audible tracheal râles. He was coughing and raising sputum containing dark red blood. His temperature was 98.4° F., pulse 100 and regular, respirations 28 and blood pressure 138/88. Respirations were labored with a prolonged expiratory phase. Throughout both lungs there was diminished resonance without definite signs of consolidation, but with numerous medium and coarse moist râles, most marked in expiration. The heart was not enlarged to percussion but the heart sounds could not be heard because of the loud respiratory sounds.

The W.B.C. was 19,000 (88% neutrophils); the hemoglobin 96%. Sputum showed gram-positive cocci and bacilli, but no acid-fast organisms. The blood non-protein nitrogen was 134 mg. per 100 cc. An electrocardiogram showed sino-auricular tachycardia, left axis deviation, upright T waves and a PR interval of 0.18. A bedside roentgenogram of the chest showed faint diffuse clouding of both lung fields with small irregular, scattered, fluffy and nodular densities.

Oxygen therapy and the usual supportive measures failed to bring about improvement and the patient died early on the morning of February 1, about 14 hours after entry.

**AUTOPSY** (14 hours after death). Only a brief description of the gross and microscopic findings in the heart and lungs is given since this case will be reported in detail elsewhere.

The heart weighed 330 gm. The auricles and ventricles were not dilated or hypertrophied. The coronary arteries showed atheromatous thickening but no actual occlusions. The interventricular septum contained a fibrous scar about 2 cm. in diameter. The valves were negative.

*Lungs.* The right weighed 1250 gm. and the left 1110 gm.. Both were subcrepitant throughout. On section, no definite areas of consolidation were seen but all lobes felt much firmer than normal. The trachea and bronchi contained a slightly mucoid, serosanguineous exudate.

*Microscopic Examination.* The *myocardium* showed large areas of scarring composed of dense collagen. There was necrosis of single muscle fibers which were invaded by large mononuclears. The interstitial tissue was infiltrated in areas with large mononuclears, lymphocytes, plasma cells, eosinophils and polymorphonuclear leukocytes (Fig. 5).

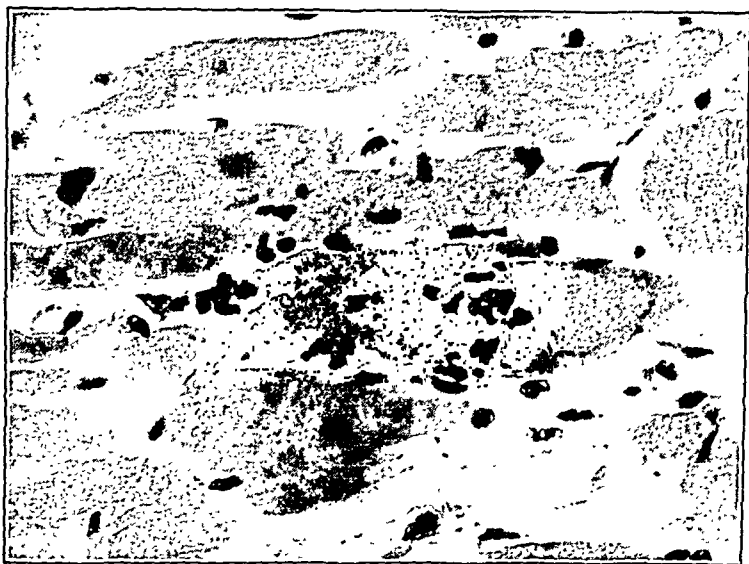


FIG. 5.—Case 2. Myocardium. Two necrotic muscle fibers invaded by large mononuclears. (Phloxine methylene blue,  $\times 750$ .)

The *lungs* throughout showed the same histologic picture. Some alveoli contained macrophages, the majority of which were filled with carbon. Other alveoli contained a small amount of albuminous precipitate, a few red blood cells and delicate strands of fibrin. Still others showed adherent to their walls a hyaline membrane in which there were often embedded a few polymorphonuclear leukocytes. The alveolar capillaries contained rather numerous polymorphonuclear leukocytes. There were also acute focal lesions in the capillaries, consisting of fibrin and neutrophils.

*Virus Isolation and Identification.* Some of the hemorrhagic portions of the lung of Case 1 were removed with sterile precautions and stored at  $-70^{\circ}\text{C}$ . in a carbon dioxide freezing box. A 20% suspension of ground-up lung was filtered through a Berkefeld "V" filter and the sterile filtrate was used for intranasal inoculation in anesthetized mice and for inoculation into the allantoic sac of 11 to 12 day old chick embryos. The first attempts were unsuccessful and were abandoned in each instance after 6 passages. A second attempt was then made beginning with a different part of the lung treated in the same manner. The mice of the first passage showed no specific lesions and 2 of 4 mice of the second passage showed minimal lesions. In the third passage 4 or 6 mice became ill on the 3rd day and died with extensive lesions on the 4th and 5th days. These 4 mice were used for further serial passage. The other 2 remained well until the 7th day and were then shown to be immune to influenza A. They were each given a challenge dose of about 100 lethal doses of PR8 virus and survived.

Virulence tests were done with the viruses of the 5th and 14th passage. The

50% lethal end-point was between  $10^{-5}$  and  $10^{-6}$  ml. with the former and between  $10^{-6}$  and  $10^{-7}$  ml. with the latter. The 38th mouse passage was again proven to be influenza A by neutralization test. A  $10^{-5}$  dilution of this virus was used. One group of mice received the virus together with serial dilutions of influenza A (PR8) ferret antiserum. All these mice survived and showed no lesions when sacrificed. The same test was done with influenza B (Lee) ferret antiserum.\* All these mice and control mice which received virus without antiserum died with typical lesions.

In the egg inoculations from this suspension of the patient's lung, the virus was well established by the 6th passage as shown by the marked and immediate agglutination of the chick cells in the allantoic fluid. Virus from the allantoic fluid agglutinated hen's red cells up to a dilution of 1:2048. The agglutination of a 1:128 dilution of the virus was inhibited by anti-influenza A (PR8) rabbit serum out to 1:1024 and by anti-influenza B (Lee) rabbit serum only in a 1:32 dilution. All of these findings establish the identity of this virus as a strain of influenza A closely related to PR8.

In Case 2, a sterile filtrate prepared from an area of hemorrhagic consolidation was inoculated into mice and eggs in the same manner as in Case 1. The first attempt in mice yielded lesions only on the 6th passage and deaths with typical lesions on the 7th passage. The 12th passage of mouse virus was fatal in  $10^{-6}$  dilution. Neutralization tests with the mouse virus and immune ferret serum showed definite protection of mice by anti-PR8 serum but not by anti-Lee B serum.

The same material injected into the allantoic cavity of eggs yielded a growth of virus in the first egg as evidenced by the agglutination of the chick cells on removal of the allantoic fluid. Egg passages were continued and virus from allantoic fluid of the 9th passage was used for identification. This virus agglutinated hen cells out to a dilution of 1:512. The agglutination of a 1:32 dilution of this virus was inhibited by anti-influenza A rabbit serum (PR8) to a dilution of 1:128 and it was not inhibited by anti-Lee influenza Type B rabbit serum in a 1:16 dilution (the lowest dilution used).

Serum obtained from the patient's heart's blood postmortem inhibited the agglutination of hen cells with PR8 virus in a dilution of 1:8 but not in 1:16.

**Discussion.** The course of events in Case 1 and particularly the possible relation of the influenza A virus to the various episodes and symptoms are difficult to interpret with the data available. The history of an influenza-like illness in December coupled with the respiratory infection in the husband who was found to have a significant titer of antibodies against influenza A after that attack, suggest the possibility that the patient's illness was also an infection with the same virus. If that were true, it might account for the persistent cough and fatigue which followed that attack, but there were no discernible anatomic changes to account for these symptoms. The lesions in the lungs were certainly of recent origin and those in the heart only somewhat older since there is no evidence of repair and fibrosis.

From a clinical point of view, two possibilities suggest themselves, both of which are based partly on speculation. The patient may have had an infection with influenza A in December and continued to harbor the virus with mild relapses from time to time until the final and fatal attack when the influenza A was isolated. In that event, the cardiac lesion, if indeed it was an influenzal viral infection, may be regarded as part of the effects of the final invasion of the virus. The

\* The anti-PR8 and anti-Lee ferret and rabbit serums were obtained from Dr. F. L. Horsfall, Jr.



alternative possibility is that the patient had a new infection from without, either at the end of February or sometime early in April, which accounted for the final illness and caused the myocardial lesion.

It is interesting, as mentioned earlier, that most of the reported clinical cases of cardiac lesions complicating influenza have occurred during convalescence and sometimes long after apparent recovery from the influenzal infections. Only rarely have such lesions, whether demonstrated at autopsy or by ECG, occurred as part of a severe and rapidly fatal acute attack of influenza. The few cases of isolated myocarditis associated with acute respiratory infections have similar time relations. The virus nature of the previously reported cases, however, is only a conjecture since viruses were not isolated. In this case, influenza A was isolated and identified. Its relation to the cardiac lesion, though only circumstantial, seems very probable.

The course and findings in Case 2 are those of an acutely fatal pneumonia complicating influenza A. The virus was obtained from the lungs which showed characteristic lesions of the virus infection. No significant bacterial pathogens could be cultured from these lungs and they did not show evidence of bacterial infection. The total duration of illness from the first symptom of a "cold" until death, was about 9 days. The pneumonia may have begun either at the time of the chills 6 days before he died or with the onset of dyspnea and cyanosis 3 days later. In the latter event, the chills may have marked the onset of the influenza. The lesions in the heart in this case were slight and limited in extent and were discovered only after careful search. Nevertheless, they were similar in character to those seen in Case 1.

The autopsy on Case 1 revealed an extensive acute myocarditis with necrosis of numerous muscle fibers, accompanied by an interstitial infiltration of various types of cells. As in some other cases reported in the past, the lesions varied from early acute necrosis to complete disappearance of the muscle fibers. There was no scar formation nor regeneration of muscle fibers. It may be of interest, perhaps, to attempt to estimate the age of the myocarditis. The histologic findings are similar to those in Schmorl's second case in which death occurred 4 weeks after an attack of influenza and also correspond to those of Roulet's first case in which death occurred 2 weeks after influenza. Covey's patient, the duration of whose illness was 13 days, had lesions in his myocardium essentially similar to those of our case. It would, therefore, seem justifiable to assume that the myocarditis in our patient was of approximately 2 to 4 weeks' duration. Such a period of time would correspond to the experience of others who state that myocarditis in influenza develops only in the late stages of the disease. That the heart was enlarged was not surprising in view of the extent of the inflammatory process, and such increases in size have been noted by other observers.

The histologic findings in the lungs deserve comment in view of the clinical picture and the fact that an influenza virus was isolated from them. As indicated in the description of the autopsy, the lungs showed surprisingly few pathologic changes. The only evidence of an acute

process was a small focus involving a few alveoli in the left upper lobe. There was no edema or hemorrhage so characteristic of influenzal pneumonitis. The fact that cultures for bacteria yielded no growth and stains for bacteria in the one inflammatory lesion seen were negative, would favor the viral etiology of this lesion.

Myocardial lesions have been described as occurring occasionally in certain virus and rickettsial diseases such as typhus fever, Rocky Mountain spotted fever, psittacosis, yellow fever, measles, mumps, variola and varicella. Myocarditis in foot and mouth disease in cattle and swine has been reported as a not unusual finding.<sup>48</sup> Furthermore, Pearce<sup>41</sup> has produced myocardial lesions experimentally in animals, utilizing for this purpose vaccinia, pseudorabies, inflammatory fibroma, strain A, and myxoma.

From the studies of some viruses, it is apparent that the myocardial lesions are due to the actual presence of the virus. However, it would seem possible that this is not necessarily true of all viruses, especially in view of the work of Rake and Jones,<sup>45</sup> who demonstrated that toxic products could be obtained from cultures of lymphogranuloma venereum.

In our case, no attempt was made to isolate a virus from the heart muscle. Since the virus of influenza is not characterized by the formation of inclusion bodies or other visible evidence of its presence, histologic examination of the lesions is of no assistance in determining whether they are due to the actual presence of the virus or its theoretically possible toxic products. The type of myocarditis resembles most closely that due to diphtheria toxin, which fact might possibly favor a toxic rather than an infectious origin of the lesions.

In Case 2, the duration of the disease was 6 to 9 days. The lesions in the heart muscle consisted of necrosis of occasional muscle fibers. In addition, there was a moderate cellular infiltration of the interstitial tissue. This patient died from his pulmonary infection, whereas Case 1 died of cardiac failure. It has been pointed out by Schmorl<sup>49</sup> that in cases of influenza dying of causes other than heart failure, it may require prolonged and diligent search for evidence of myocardial damage. This statement would seem to hold true here. The lesions, while comparatively few in number, differ from those of Case 1 only in their rarity, not their type. In Case 2, as in Case 1, cultures yielded no bacteria, but a virus was isolated from the lungs. Histologically, there was no evidence of bacterial infection of the lungs, but the picture was that of an acute influenzal pneumonitis.

**Summary and Conclusions.** 1. Two cases with pathologic findings of acute non-bacterial myocarditis are reported. One of these patients died of cardiac failure and had a minimum of involvement of the lungs; the other died of an extensive acute bronchopneumonia from which no significant bacterial pathogen could be recovered. Influenza A virus was isolated from the lungs of both cases.

2. A review of the literature concerning the clinical and pathologic aspects of acute myocarditis complicating influenza and similar respiratory infections is presented. The relation of the influenza virus to the cardiac lesions in the present cases is discussed.

3. It is suggested that the myocardial lesions in these cases are the result of infection with influenza A virus.

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## PROVOCATIVE PROLONGATION OF THE P-R INTERVAL IN RHEUMATIC FEVER\*

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THE clinical recognition of cardiac involvement in acute rheumatic fever frequently is very difficult. Numerous studies have established the value of the electrocardiogram as the most sensitive and dependable indicator of cardiac involvement in rheumatic fever. Murmurs, enlargement of the heart, gallop rhythm, pericardial effusion and other clinical findings occur in only a small minority of cases in the initial stages of carditis and so are of rather limited diagnostic value.

The most frequent and most specific electrocardiographic sign of carditis is impairment of atrio-ventricular conduction, *i. e.*, prolongation of the P-R interval. The frequency of prolongation of the P-R interval varies greatly in published reports. It is generally recognized that this sign is inconstant and frequently transitory. Even where serial or even daily tracings are employed, a procedure hardly practical as a routine, prolongation of the P-R interval is detected in only about one-half of cases, averaging the reports of various investigators.<sup>9</sup>

It is our purpose to report a simple procedure which appears to enhance the diagnostic value of prolongation of the P-R interval in acute rheumatic fever.

A study of the effect of carotid sinus pressure on the P-R interval was carried out in 16 cases with rheumatic fever, and in 16 control subjects who were hospitalized for miscellaneous infectious diseases, such as scarlet fever, pneumonia, and upper respiratory infections. Electrocardiograms were recorded during right, left, and bilateral carotid sinus pressure both in sitting and recumbent positions. In most cases similar studies were also carried out 20 minutes following intramuscular administration of 1 cc. of 1:2000 prostigmin.

In none of the control subjects did any prolongation of the P-R interval exceeding 0.01 second more than the control occur on carotid sinus stimulation with or without prostigmin. On the other hand, definite prolongation of the P-R interval was observed in 12 of the 16 cases with rheumatic fever. In 2 of the 4 cases with rheumatic fever in whom no prolongation of conduction occurred prostigmin was not given; and as will be shown prostigmin augments the effect in many cases.

\* Presented at the New York Heart Association, May 2, 1944.

**Case Illustrations.** CASE 1 (Fig. 1). H. G., a boy of 13, developed acute rheumatic fever in May 1942. Signs of activity persisted for 3 months with residual mitral insufficiency, as indicated by an apical systolic murmur and slight backward displacement of the esophagus revealing early left atrial enlargement. The P-R interval which varied between 0.20 to 0.28 second remained prolonged for a period exceeding 18 months after all other signs of

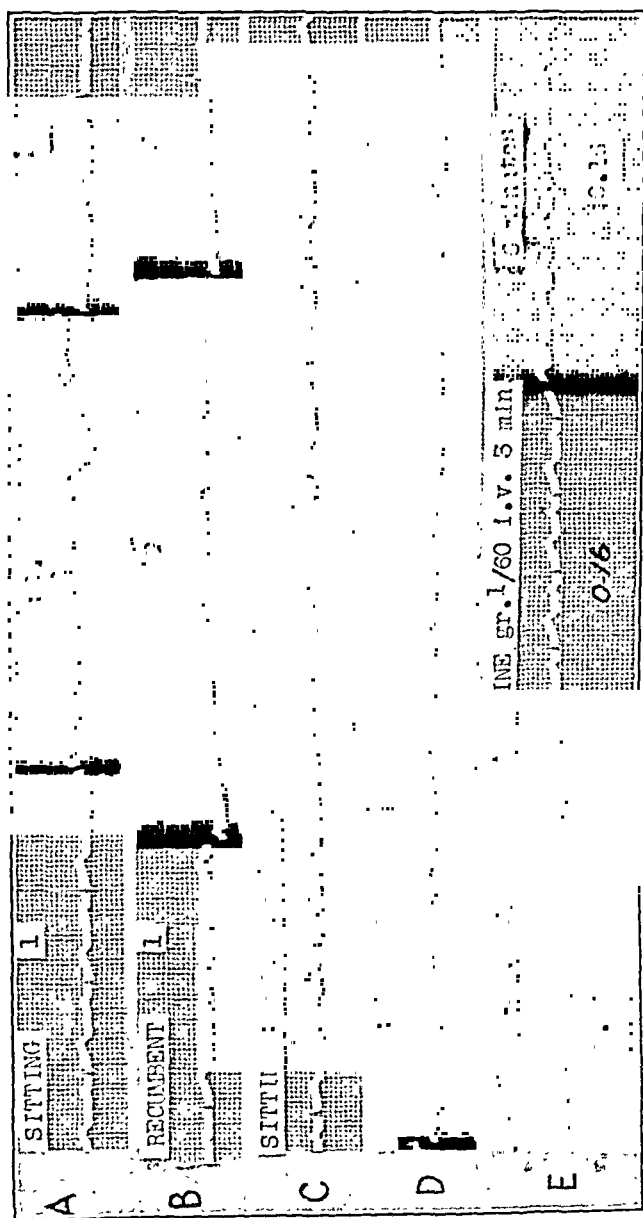


Fig. 1.—Case 1. P-R interval prolongs to 0.28 second in recumbent position (B), normal (0.18 second) in sitting position (A). Pressure on left carotid sinus (D) in sitting position prolongs P-R from 0.18 to 0.30 second, whereas right carotid pressure (C) is without effect on conduction time. Atropine (E) given intravenously promptly shortens P-R to 0.16 second.

rheumatic activity had subsided. The persistent prolongation of the P-R interval was evident only in the recumbent position, conduction being within normal limits when sitting. Pressure on the left carotid sinus, but not on the right, increased the P-R interval from 0.18 to 0.30 second in the sitting position. The prolonged conduction was abolished promptly by intravenous administration of 1 mg. of atropine.

While in Case 1 the changes in atrio-ventricular conduction occurred when other evidences of active carditis no longer were present, more frequently, as illustrated in Figure 2, the effect of carotid pressure in prolonging the P-R interval is maximal in the initial acute stages of carditis and can no longer be elicited after signs of rheumatic activity have subsided.

CASE 2 (Fig. 2). R. V., a male, age 20, gave a history of a previous attack of rheumatic fever 5 years before. He was hospitalized on Feb. 29, 1944, because of fever and polyarthrits involving the right knee and both ankle joints. These symptoms began 3 days before admission and 2 weeks following a cold and sore throat. On examination a systolic apical murmur was heard, pulse rate was 104, leukocyte count 12,300, sedimentation rate 108 mm. in 1 hour, and blood ascorbic acid level reduced to 0.3 mg. per 100 cc. The electrocardiogram (Fig. 2) showed a slight prolongation of the P-R interval to 0.21 second with increase in conduction to 0.24 second on right carotid pressure in the sitting position. A second electrocardiogram 4 weeks after admission, at which time clinical evidence of rheumatic activity had subsided showed a P-R interval of 0.17 second, with no change in carotid pressure. Further electrocardiographic study on April 8, 1944, similarly showed normal atrio-ventricular conduction with no prolongation on carotid pressure or on pressure after intramuscular administration of 1 cc. of 1:2000 prostigmin.

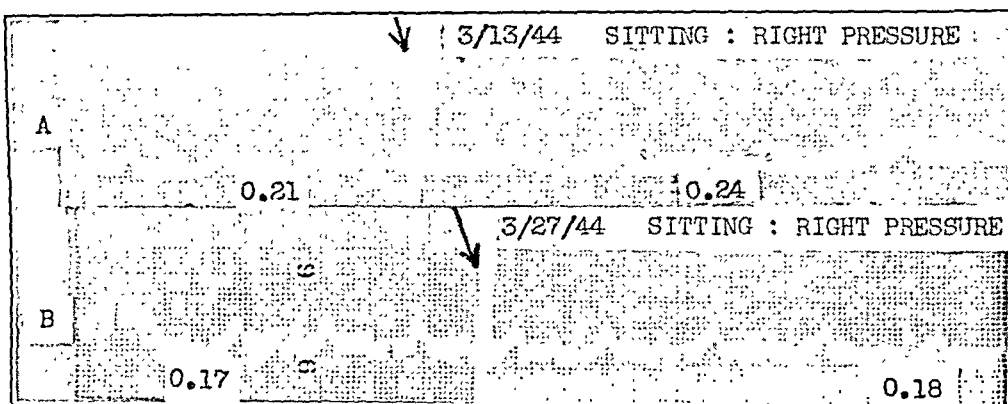


FIG. 2.—Case 2. A, Application of carotid pressure (arrow) abruptly lengthens P-R from 0.21 to 0.24 second. B, Repetition of carotid pressure test after subsidence of signs of acute carditis shows no effect on conduction time.

Usually, as illustrated in Figure 3, the effect of carotid pressure is greater on the left than on the right, and in the sitting more than in the recumbent position.

CASE 3 (Fig. 3). R. M., male, age 26, 3 weeks after scarlet fever, developed polyarthrits and an accelerated sedimentation rate. An electrocardiogram a few days after admission to the hospital was normal, the P-R interval measuring 0.20 second. In the sitting position pressure on the right carotid sinus prolonged conduction to 0.24 second. Pressure on the left caused even greater prolongation to 0.36 second. One month after discharge from the hospital the carotid pressure test was repeated. The P-R interval was unaffected and did not become prolonged on carotid pressure following administration of prostigmin.

Occasionally prolongation of the P-R interval occurs only on right and not on left carotid pressure, although more often the reverse is true.

CASE 4 (Fig. 4). R. R., a male of 18, was hospitalized on March 7, 1944, with an onset of polyarthrititis 3 days before admission. Leukocyte count was 12,000, sedimentation rate 80 mm. settling in 1 hour, blood ascorbic acid level 0.5 mg. per 100 cc. An apical systolic murmur was present. The P-R interval measured 0.20 second. Pressure on the left carotid sinus did not affect the conduction time but pressure on the right carotid sinus prolonged the P-R interval from 0.20 to 0.28 second, with transient slowing of the heart rate.

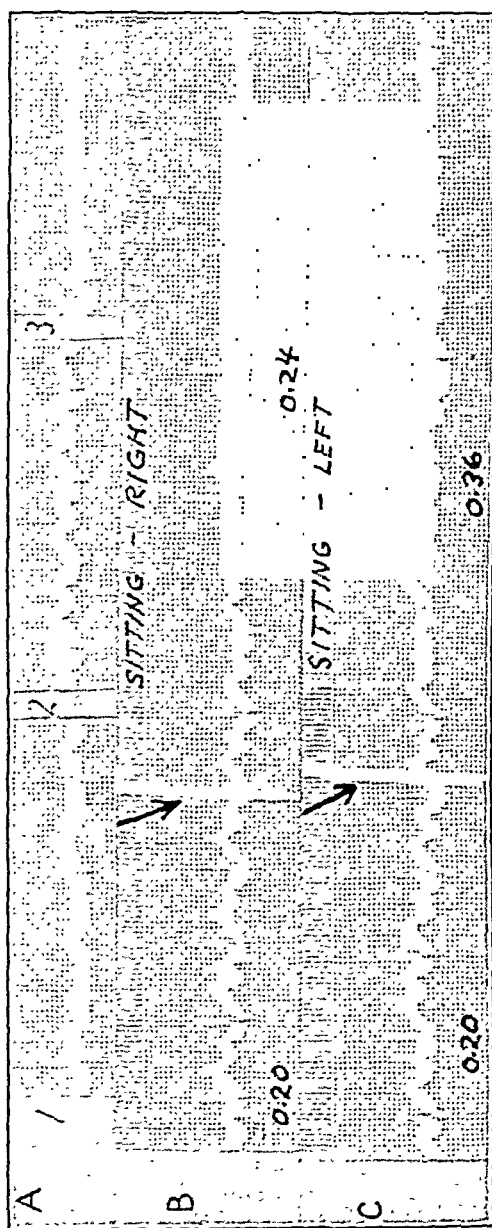


FIG. 3. Case 3. Pressure on left carotid sinus (C) prolongs P-R interval from 0.20 to 0.36 second. Right carotid pressure (B) causes less marked prolongation to 0.24 second.

CASE 5 (Fig. 5). V. B., male of 18 years, was hospitalized on Feb. 10, 1944, because of polyarthrititis developing after a sore throat. Leukocyte count was

elevated to 14,800, sedimentation rate was 80 mm., settling in 1 hour. Apart from tachycardia there were no abnormal cardiac findings. The ECG was negative except for slight right axis deviation which could be attributed to

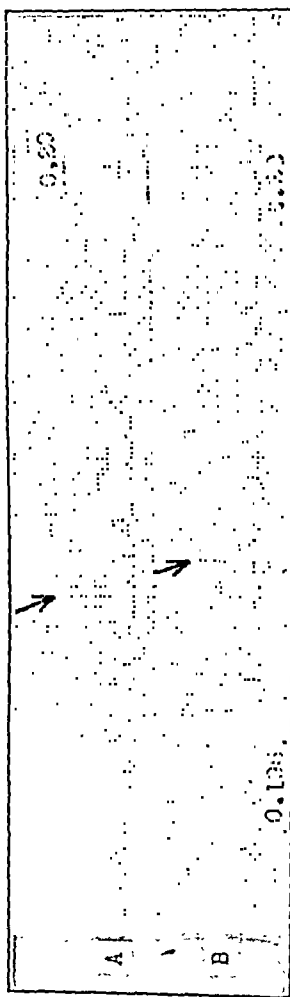


Fig. 4.—Case 4. Left carotid pressure (A) has no effect on conduction time, whereas right carotid pressure (B) prolongs the P-R to 0.23 second.

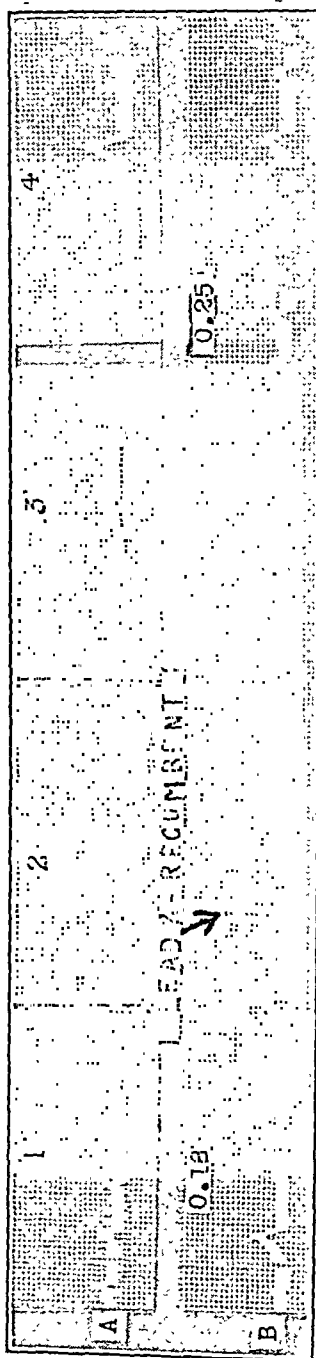


Fig. 5.—Case 5. A, Normal electrocardiogram in case of acute rheumatic fever. Right axis deviation is present. B, Pressure on the right carotid sinus in the recumbent position prolongs the P-R interval from 0.18 to 0.25 second. The amplitude and width of the P waves are increased during pressure.

slender body build. Pressure on the right carotid sinus in the recumbent position prolonged the P-R interval from 0.18 to 0.25 second. Two months later, at which time all signs of rheumatic activity had subsided, the test was



repeated and no prolongation of the P-R interval could be induced by pressure, or pressure plus prostigmin.

Where carotid sinus pressure alone is ineffective preliminary intra-muscular administration of 1 cc. of 1:2000 prostigmin 20 minutes

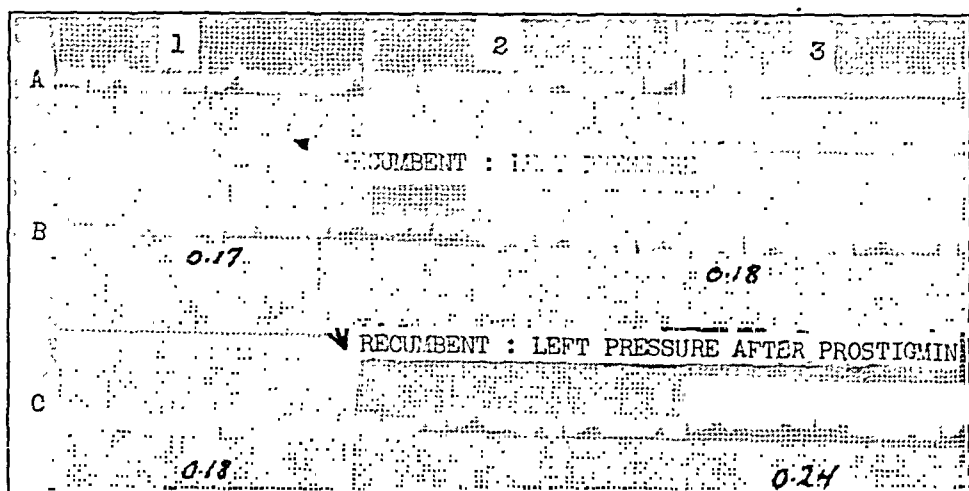


FIG. 6.—Case 6. A, Normal electrocardiogram in subject with acute rheumatic fever. Pressure on the left carotid sinus (B) is without effect on conduction, but following prostigmin (C) left carotid pressure prolongs the P-R interval from 0.18 to 0.24 second.

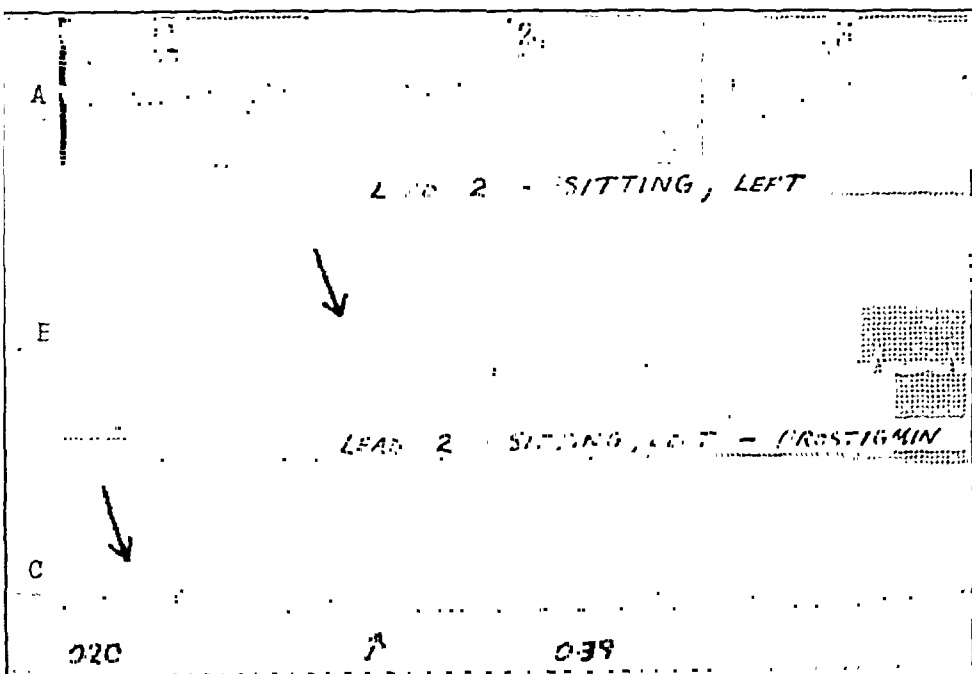


FIG. 7.—Case 7. A, Pressure alone in this subject with acute rheumatic fever and pericarditis is without effect on conduction (B). Following prostigmin (C) left carotid pressure prolongs the P-R from 0.20 to 0.39 second with dropped beats.

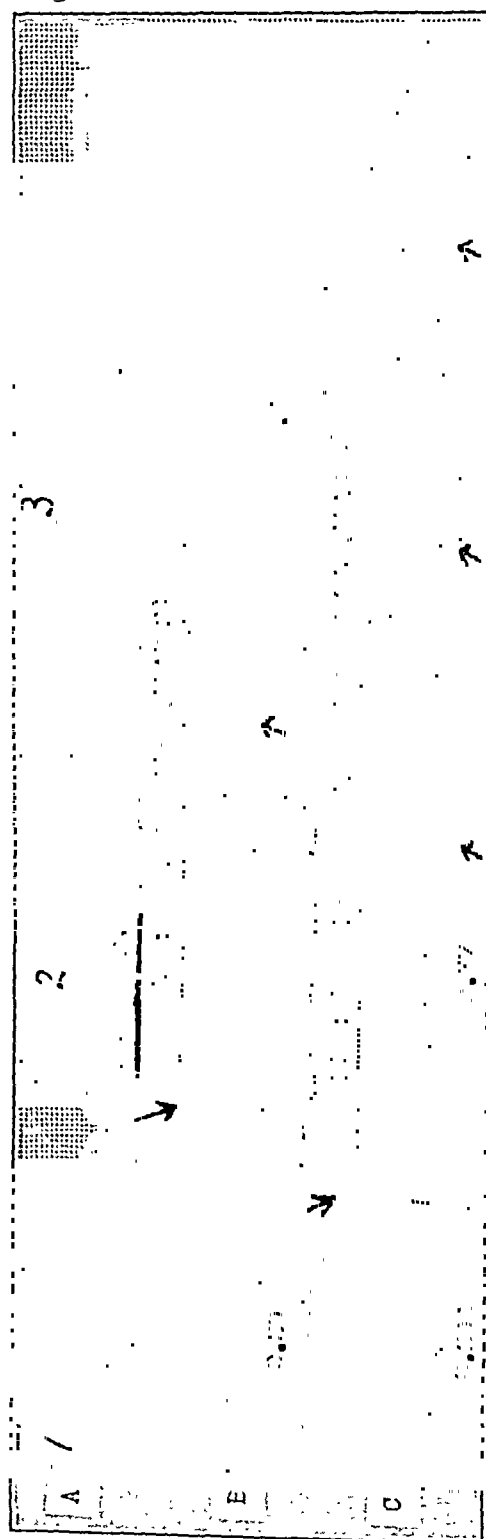


Fig. 8.—Case S. A, Control electrocardiogram is normal. B, Following left pressure P-R lengthens from 0.20 to 0.37 second, with dropped beat. C, After prostigmin left carotid pressure causes 2 to 1 partial heart block with marked prolongation of the P-R in the conducted beats.

before the test may serve to induce prolongation of the P-R interval on carotid pressure. In none of the cases studied did prostigmin alone prolong atrio-ventricular conduction.

CASE 6 (Fig. 6). E. D., a male, age 27, was hospitalized March 14, 1944, because of polyarthritis of 5 days duration. Leukocyte count was 12,000 and blood ascorbic acid was reduced to 0.4 mg. per 100 cc. There were no abnormal cardiac findings and the ECG (Fig. 5) was normal. Pressure alone did not appreciably alter the P-R interval but when repeated 20 minutes following the intramuscular administration of prostigmin the P-R interval became prolonged from 0.18 to 0.24 second. Five weeks later, at which time the patient had been discharged and all signs of rheumatic activity had subsided, prostigmin and carotid pressure had no effect on the P-R interval, such as occurred during the acute stage of rheumatic fever. .

The effect of prostigmin plus carotid pressure is shown even more strikingly in Figure 7. Pressure alone had little effect but following prostigmin marked prolongation from 0.20 to 0.39 second; with dropped beats, occurred on carotid pressure.

CASE 7 (Fig. 7). R. S., a female, age 29, was hospitalized because of a nodular erythema of the lower extremities, arthralgias and fever. Tachycardia and gallop rhythm were present and precordial pain and a friction rub indicated pericarditis. T-wave changes in the ECG were present. The P-R interval, which measured 0.20 second, was unaffected by carotid pressure alone, but following prostigmin carotid pressure induced partial heart block, with the P-R interval prolonged to 0.39 second.

Even more striking partial heart block induced by pressure, and pressure plus prostigmin is illustrated in Figure 8.

CASE 8 (Fig. 8). R. B., a male, age 18, was hospitalized Feb. 21, 1944, for migrating polyarthritis developing 2 weeks following a sore throat. Fever, tachycardia, leukocytosis (W.B.C. 13,000), accelerated sedimentation rate (70 mm. in 1 hour) and low blood ascorbic acid (0.3 mg. per 100 cc.) were present. An apical systolic murmur was heard. The ECG was normal, the P-R interval measuring 0.20 second. Pressure on the left carotid sinus in the sitting position prolonged conduction to 0.37 second, with one dropped beat. Following prostigmin left carotid pressure induced 2 to 1 partial heart block with prolongation of the P-R interval to 0.37 second. A subsequent test of this subject, carried out at the time of discharge for convalescent care, was entirely negative, with no effect from pressure, or pressure plus prostigmin.

**Comment.** Bruenn,<sup>1</sup> Keith,<sup>6</sup> and others<sup>13</sup> have shown that the prolongation of the P-R interval in rheumatic fever frequently can be abolished by atropine. This suggests that the impairment of atrio-ventricular conduction is in many cases due to a heightened vagal effect rather than to an intrinsic defect in the conduction mechanism. Our own experiments showing the increased sensitivity to vagal stimulation are further evidence for this view. This does not necessarily signify a greater vagal tone as such. The action of the vagus is determined, not only by the release of acetyl choline, but also by the rate of destruction of acetyl choline by the tissue enzyme choline esterase, as first shown by Loewi and Navratil.<sup>7</sup>

The activity of choline esterase is greatly modified by the pH, its action being maximal in an alkaline medium and falling sharply as

the pH shifts toward the acid side as Glick<sup>3</sup> has demonstrated. If the maximum choline esterase activity at pH 8.4 be considered as 1, the activity at pH 8 is 96%; at pH 7, 49%; at pH 6, 16%. Inflammatory tissue as Schade,<sup>11</sup> Valy Menkin,<sup>8</sup> and others have shown is characterized by a lowering of pH, due to accumulation of acid metabolites. Heymans and his co-workers,<sup>5</sup> Richard,<sup>10</sup> and recently Smith and Wilson<sup>12</sup> have shown further that the heart is rendered much more sensitive to the action of acetyl choline by anoxemia, which presumably likewise acts by decreasing the pH in the myocardium inhibiting the effect of choline esterase.

Gross and Fried,<sup>4</sup> in a study of lesions in the atrio-ventricular conduction system occurring in rheumatic fever, have shown that in two-thirds and probably more of cases with rheumatic fever coming to autopsy, "a variety of inflammatory and vascular phenomena within the horizontal conduction system as well as in the surrounding tissues" occur. We suggest that the inflammatory process and vascular changes in the region of the conduction system, by lowering the pH and interfering with tissue nutrition inhibit choline esterase, allowing potentiated vagal effect, which is responsible for prolongation of atrio-ventricular conduction.

**Summary.** 1. Carotid stimulation prolongs the P-R interval very frequently in acute rheumatic fever.

2. The effect is more marked when the P-R interval is initially 0.18 to 0.20 second than when it is less than 0.18 second, vagal stimulation intensifying latent impairment in atrio-ventricular conduction.

3. The effect of carotid pressure on conduction is maximal during the acute stage of carditis, and frequently disappears as rheumatic activity subsides.

4. Prolongation occurs more commonly in the sitting than in the recumbent position, and more often with left than with right carotid pressure.

5. In many cases the effect is augmented by preliminary administration of prostigmin. Prostigmin alone, in the dose employed, does not prolong the P-R interval. Dameshek, Loman and Myerson<sup>2</sup> likewise observed that prostigmin has no effect on the P-R interval. Mecholy, however, as reported by these investigators, may considerably prolong atrio-ventricular conduction in normal subjects.

**Conclusions.** 1. Impairment of atrio-ventricular conduction of considerable degree was induced in 12 of 16 subjects with rheumatic carditis by pressure on the carotid sinus. Similar pressure has produced no such impairment in 16 control cases.

2. Preliminary administration of prostigmin augments the response in many cases.

3. The effect is more marked when the P-R interval is initially 0.18 to 0.20 second than when it is less than 0.18 second.

4. The changes in conduction are maximal during the acute stages of carditis and tend to disappear as rheumatic activity subsides.

5. It is suggested that this procedure enhances the diagnostic value of prolongation of the P-R interval in rheumatic fever.

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## THE PRIMARY INFLUENCE OF BASAL VASCULAR TONE ON THE DEVELOPMENT OF POSTOCCLUSIVE COLLATERAL CIRCULATION AND IN SELECTING PATIENTS FOR SYMPATHECTOMY

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WHILE routinely determining the basal vascular tone\* of patients with major peripheral arterial occlusions it became evident that the grade of the individual's general peripheral vascular tone played a decisive rôle in the development of a collateral circulation.

Despite general recognition of the importance of collateral circulation following a major peripheral arterial occlusion, very little is known of the factors determining its development. The present study offers objective evidence of a physiologic mechanism which operates to aid or to hinder the development of a collateral circulation in accordance with the individual's intrinsic vascular tone.

Although our observations are in contradiction to Lewis'<sup>4</sup> own concept of collateral circulation, we feel it is important to quote the following passages by him at length because they summarize so well the conflicting views on this subject:

"When a main artery to a limb becomes blocked, certain factors come into play, at once or after very short delay, and tend to restore the circulation to the distal tissue. As Recklinghausen pointed out there is, as a result of the obstruction, a little rise of pressure proximal to it, while there is a decided fall of pressure in the artery and its branches distal to it. These immediate changes in pressure increase the flow in branches issuing from the main artery proximal to the obstruction and supplying the territory in which the pressure

\* Tone has been defined as the resistance muscle offers to stretch. This is analogous to our definition of vascular tone which is the ability of blood-vessels to constrict and to resist vasodilatation.

is lowered. Moreover, as Bier concluded, the vessels of the deprived territory will enter a state of reactive hyperæmia, owing as we should now say to the accumulation of vasodilator substances in the corresponding tissues.

"These early adjustments help to restore circulation. They are, however, inadequate to explain the formation of permanently enlarged channels. Thoma concluded on the basis of many observations that such growth of collateral channels occurs because blood flow through them is increased. In this he was supported by Nothnagel, who also expressed the view that the vascular growth is due to increased nutrition consequent upon increased flow through the vessel affected, or consequent upon increased flow through its vasa vasorum. It is to be noted that such collateral anastomoses develop whether the limb is previously deprived of nerves or not; the development is independent of nerve supply. Thoma's theory, that the growth or shrinkage of arteries is controlled by the amount of blood flowing through them, might be held adequately to explain the development of collateral channels when the main artery of a limb is obstructed."

In attempting to clarify the understanding of the mechanisms underlying the development of collateral circulation in general, Lewis drew upon his observations on arteriovenous fistulæ and further states:

"... and we are brought to ask if arterial growth is not directly controlled by a stimulant, a chemical stimulant arising locally as a product of the tissue need, and acting locally. The growth of collateral channels is so locally adjusted and occurs under such different circumstances of pressure and flow, that it now seems quite necessary to formulate an intimate and special mechanism to explain this permanent increase in size. The essence of the matter seems to be that there is a local call by tissues in need and that to this call there is a local and adequate response."

Lewis' concept, which is generally accepted,<sup>6</sup> does not seem entirely valid in view of our observations. If ischemia were the predominating stimulus for promoting a collateral circulation, individuals with high vascular tone with a major arterial occlusion, should develop a collateral circulation because of the severity of their ischemia, as in them there is certainly an intense "local call by tissues in need." Since they usually do not develop a collateral circulation, ischemia cannot be considered the principal stimulus to its development. We were finding that patients with a popliteal or femoral occlusion who had a low grade of vascular tone or relaxed peripheral vessels, as determined by the behavior of the vessels in the hands, almost invariably developed a collateral circulation, whereas similar patients with a high grade of vascular tone were very unlikely to develop their collaterals, and as a consequence their symptoms were much more severe.

Vascular tone tests have shown us that an individual's own particular grade of vascular tone, whether it be low tone or high, is the predominating influence on his ability to develop a collateral circulation. It may be that vascular tone acts, though in part only, in much the same manner as the mechanisms described by Thoma and Nothnagel. Their conclusions are, nevertheless, entirely inadequate to describe the conflicting responses in different patients with the same degree of arterial occlusion. At that time there was no objective method of measuring an individual's basal vascular tone, nor was the normal range known or considered as of primary importance in an individual

with a major peripheral arterial occlusion. It is only recently that it has been recognized that a constant gradient is maintained between the vascular tone in the hands and that in the feet. Consequently Nothnagel in 1889 and Thoma in 1896, though their observations were probably true in part, failed to account for the conflicting variety of responses in different patients with the same degree of peripheral arterial occlusion.

Our method of grading vascular tone is described in detail in a recent paper,<sup>5</sup> where 270 normals and patients were classified in 7 groups. For the purpose of this special study of collateral circulation it is sufficient to classify the patients into the two basic groups of high and low vascular tone, which can be determined by observations of the temperature responses in the hands alone. We regard an individual as having a high grade of vascular tone if the hands are cool (below 25° C.) 15 minutes after the patient has been in a constant temperature room at 20° C., unclothed except for a light gown. This individual's peripheral vessels are easily constricted. If, on the contrary, the hands remain warm (25° C. or above) after this same exposure, the patient is in a low vascular tone group. This individual's peripheral vessels are easily relaxed. For this test to be reliable the patient must be in a basal state at the start of the test, having omitted the preceding meal and any hot drinks, drugs, or hot bath that might induce vasodilatation. In cold weather (below 55° F.) subjects should be kept in a warm room for 30 minutes before starting the test. Since most of the patients discussed in this paper have occlusions of the major arteries of both legs, the toe temperatures were not considered when grading vascular tone, but were observed as the important indication of the presence or absence of collateral circulation.

In this study we determined the grade of vascular tone and its relationship to the incidence of collateral circulation and to the severity of symptoms in 70 patients with occlusions of the femoral or popliteal arteries. In 38 of the patients the occlusion was due to arteriosclerosis, in 30 it was due to thrombo-angiitis obliterans and in 2 due to embolism. Forty-four (63%) of the patients had a low grade of vascular tone and 26 (37%) had high vascular tone. Eighteen of the 30 patients with thrombo-angiitis obliterans had a low grade of vascular tone. Of the 38 patients with arteriosclerosis, 24 had a low grade of vascular tone.

Of the 44 patients with low vascular tone and with major occlusions, 38 (88%) had developed an excellent collateral circulation, some without any therapy. Of the remaining 12%, only 1 patient had an old occlusion. The others who did not have collaterals in this low tone group had a history of very recent occlusions. We have found clinically that some patients with bilateral occlusions had an adequate collateral circulation in the extremity with the oldest history of an occlusion, whereas the other leg with the recent occlusion had the inadequate blood flow of an undeveloped collateral circulation. It is our feeling that these patients in the low tone group will eventually establish an adequate collateral circulation in both extremities,

as have the great majority of the individuals with low vascular tone. Eckstein, Gregg and Pritchard<sup>2</sup> found that it took weeks for a complete collateral circulation to develop in experimental occlusion of the femoral arteries in dogs. Of the 26 patients with a high grade of vascular tone, only 9 (34%) had developed an adequate collateral circulation, and in half of these patients a posterior tibial nerve block with procaine was necessary before any dilatation of collaterals could occur.

We then reviewed the histories of these patients taken prior to this investigation, and recorded the incidence of severe symptoms (claudication at a half-block or less) and the presence or absence of gangrene or amputations. These findings were then related to the patients' grade of vascular tone. Whereas 17 of the 26 (65%) of the patients with high vascular tone had severe claudication, this was present in only 10 of the 44 (23%) of those with low vascular tone. A similar increase was found in the percentage of gangrene and amputations in the patients with a high grade of vascular tone.

These findings suggest that ischemia is not an effective stimulus in the development of a collateral circulation in patients with high vascular tone. In this investigation it appears that the grade of an individual's basal vascular tone plays the decisive rôle in encouraging or discouraging the development of a collateral circulation following a major peripheral arterial occlusion, probably because dilatation is the more frequent state of the collaterals in the individual with low vascular tone, and resistance to vasodilatation is the more frequent state in the individual with high vascular tone.

There was no correlation between the amount and type of therapy given to these patients and the development of a collateral circulation in the two vascular tone groups. Many with high vascular tone had treatment such as suction and pressure, the vaso-oscillating bed and forms of vasodilator therapy, including fever therapy, and yet had not developed a collateral circulation, though the elapsed time would have been sufficient for the development of collaterals in an individual with low vascular tone. Many of these patients whose basal vascular tone is high had their occlusions several years prior to this study. In the group with low vascular tone many had no therapy at all before they were seen by us, yet they had already developed collaterals. These findings explain why clinical results reported with new forms of therapy for peripheral vascular disease are so often unreliable. Until the natural course of an arterial occlusion is studied in individual patients by determining their vascular tone, one cannot attribute improvement to any form of therapy without the question arising as to whether or not improvement has been the spontaneous result of a combination of low vascular tone and the passage of sufficient time for the development of a collateral circulation.

The results of this analysis show that therapy, but not radical therapy, is indicated for the individual with low vascular tone with a major peripheral arterial occlusion. Often an instruction sheet on care of the feet is all that is necessary for these patients. If the occlu-



sion is recent, a short course of suction and pressure and mild vasodilator therapy is usually sufficient treatment until they have established an adequate collateral circulation. On the other hand, the patient with high vascular tone and no collateral circulation needs the benefit of the most intense and constant vasodilator therapy, often including sympathectomy.

When the striking difference in the natural course of major peripheral arterial occlusions was observed between the two groups of patients with low and high grades of vascular tone, we began recommending sympathetic ganglionectomy only in patients with a high grade of vascular tone. The wisdom of this method of selecting patients for sympathectomy was confirmed when we saw 2 patients with low vascular tone who had been sympathectomized prior to this investigation and who had an increase in the severity of their symptoms, probably as the result of too great a diversion of blood from the toes to vessels in the thigh and leg which had perhaps been dilated before the sympathectomy. Freeman and Montgomery,<sup>3</sup> in discussing lumbar sympathectomy in the treatment of intermittent claudication, describe an analogous situation. In 1 of the patients they discuss, following sympathectomy there was a marked increase in oscillations at the calf and a decrease in oscillations at the ankle after exercise, reflecting a diversion of blood from the foot. Atlas<sup>1</sup> has recently reported development of gangrene in 3 patients in whom lumbar sympathectomy had been done for peripheral arteriosclerotic disease. He believed that in these patients surgically induced relaxation of flexible arteriovenous anastomoses in an ischemic foot could shunt blood from the capillary bed in sufficient quantity to cause tissue necrosis and gangrene.

To us it seems irrational to sympathectomize an individual who has a low grade of vascular tone below the knee, since his collaterals are already in a state of vasodilatation or are in the process of developing, and one risks the hazard of diverting blood from the foot, the site where gangrene is most likely to develop. However, the patients with high vascular tone and whose symptoms are not improving or are becoming more severe deserve the benefit of immediate sympathectomy, regardless of whether the cause of the occlusion be thromboangiitis obliterans, arteriosclerosis or ligation of a major artery following injury. We now recommend sympathectomy in the latter group of patients, even though some have not vasodilated with procaine block of the posterior tibial nerve and the results have been uniformly good, with the exception of 1 patient who had a foot already in a hopeless state of gangrene when he was first studied.

By selecting the patients who are suitable for sympathectomy on the basis of their responses during the vascular tone test, the operation may find a more definite place in the treatment of arterial occlusive disease. Hitherto, patients who did not have a rise in toe temperature in response to a nerve block were not considered suitable candidates for sympathectomy because they lacked the capacity for vasodilation in response to procaine. Yet these patients are in the high vascular tone group who need sympathectomy most and who, in our experience,

are most benefited by the procedure. Sympathectomy in such cases, by creating a state of low tone of the arteries above the occlusion, encourages the establishment of a collateral circulation in the same manner as it occurs spontaneously in the individual with low vascular tone. In these patients, sympathectomy not only lowers the tone of the vessels above an occlusion and thereby increases the pressure stimulus for opening the collateral vessels, but at the same time lowers the tone of the collateral vessels themselves.

**Conclusions.** 1. An objective method is described by which, for the first time to our knowledge, one can predict whether a collateral circulation is likely to develop following a major peripheral arterial occlusion and whether a sympathetic ganglionectomy is indicated.

2. By determining the patient's basal vascular tone, which can be obtained from any unoccluded extremity, we are able to predict far more accurately the course of the disease, and to decide the amount and type of treatment required.

3. Patients who have a low grade of vascular tone will develop a collateral circulation almost invariably and, as a rule, do not require much active treatment.

4. The majority of patients who have a high grade of vascular tone do not develop a collateral circulation; and, since their symptoms are much more severe, require intensive treatment.

5. Only patients with a high grade of vascular tone require sympathetic ganglionectomy.

6. The previous method for selecting patients for sympathectomy on the basis of their capacity to vasodilate in response to paravertebral or local nerve block is erroneous. The patients who are in most urgent need for sympathectomy are those with high basal vascular tone who do not respond to temporary nerve block.

7. Patients with low vascular tone are not improved by sympathetic ganglionectomy.

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### A FATAL CASE OF CEREBRAL COCCIDIOIDOMYCOSIS WITH CULTURAL STUDIES

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COCCIDIOIDOMYCOSIS is a respiratory infection, usually self-limited, that follows inhalation of the chlamydospores of *Coccidioides immitis*. About 5% of the patients develop a toxic rash 2 or 3 days after onset,

followed by an erythema nodosum<sup>14</sup> often associated with polyarthritis. The disease is endemic in south central California, particularly the San Joaquin Valley, the southern half of Arizona, and western Texas. Several reviews of the literature on pulmonary coccidioidomycosis have appeared recently,<sup>11,12,17</sup> for the disease has become of increasing importance since large numbers of troops have been stationed in these areas.

In about 0.05% of cases<sup>8</sup> the pulmonary manifestations are followed by widespread hematogenous dissemination of the fungus. Miliary tubercles and confluent areas of caseation necrosis have been found in all of the visceral organs, the skin, joints,<sup>12</sup> and meninges of the brain and spinal cord. This generalized infection, called coccidioidal granuloma, is the only form in which the disease was known to medicine for over 40 years. Not until the publication of Dickson's paper in 1937<sup>7</sup> was it recognized that this illness, which carries a mortality of 50%, is an uncommon complication of the benign respiratory disease locally known as "San Joaquin fever."

In 1936 Abbott and Cutler<sup>1</sup> reviewed the literature of central nervous system coccidioidomycosis and found reports of 23 cases to which they added 11 of their own. The most common lesion was a basilar meningitis. In 2 instances there was an associated small intracerebral granuloma; in the first it was located in the right cerebral hemisphere, in the second a 4 mm. nodule was found in the right optic thalamus. Courville and Abbott<sup>5</sup> reported 5 additional cases of meningitis in 1 of which there was also a "small area of involvement of the superficial cortex." These authors point out that coccidioidal granuloma very rarely results in lesions within the nervous tissue itself. This is quite remarkable in view of the great frequency of meningitis (25%) in cases of disseminated coccidioidomycosis. A 4th case with a cerebral lesion was reported by Craig and Dockerty<sup>6</sup> who describe a granuloma 1 cm. in diameter in the left cerebellar hemisphere.

At the Army Institute of Pathology in Washington there are, at the time of writing, records of 23 autopsied cases of coccidioidomycosis in which the brain and meninges had been examined. With the exception of a male civilian, all were soldiers stationed in endemic areas during and after 1941. A basilar meningitis was found in 13 instances. In one of these there was an associated direct extension of the lesion into the underlying brain substance; in another a miliary granuloma in the substantia nigra (Cases 12 and 13, Table 1). Two cases (Cases 14 and 15) had intracerebral lesions without an accompanying meningitis. Equal numbers of white and Negro soldiers showed central nervous system involvement. This should not be interpreted as contrary to the accepted opinion that the disseminated form of coccidioidomycosis is much more common in the colored races, since the number of white troops stationed in endemic areas far exceeds that of Negro troops.

The rarity of invasion of nervous tissue by *C. immitis* when compared with its relatively high incidence of meningitis is in marked contrast to the lesions seen in blastomycosis where granulomata are

TABLE 1.—OBSERVATIONS IN 15 CASES OF COCCIDIOIDOMYCOSIS WITH INTRACRANIAL LESIONS

Case No.	A.M.M.* Acc. No.	Age	Race	Systemic involvement	Duration of infection (mos.)	Duration of meningeal symptoms (mos.)	Spinal fluid findings	Leptomeninges	Brain
1	68315	32	B	Lungs	10	10	No record	Thickened at base and over cord	Normal
2	74601	40	W	D†	9	2	Wassermann 2+, WBC 2000, mostly lymphos; gold curve 555544210	Fibrinous exudate and fibrinous adhesions about base	Normal
3	77804	35	Y	Lungs	10	1	WBC 200, neutrophils 28%, lymphos. 72%; gold curve 2355432100	White granules about base of cbr., cbl. and parietal lobes	Normal
4	78078	35	W	D	4½	2	WBC 440, neutrophils 66%, lymphos. 34%, gold curve 5555432000	Thickened about base; few small nodules over parietal lobes	Normal
5	90363	35	B	Lungs mediast. ly. nodes	6	3	WBC 300, neutrophils 20%, lymphos. 80%, gold curve 2225422100	Fibrinous plaques at base	Normal
6	92498	21	W	Lungs	5	5	WBC 692, neutrophils 7%, lymphos. 93%, gold curve 555554331	Thickened about base and over cord	Normal
7	97165	27	W	D	2	2	WBC 340, neutrophils 40%, lymphocytes 60%	Pale yellow gelatinous exudate about base	Normal
8	97521	31	B	D	2½	½	No record	Thickened and granular about base	Normal
9	104135	37	W	None	6½	6½	WBC 690, neutrophils 13%, lymphos. 87%	Fibrinous, granular exudate about base	Normal
10	105308	27	B	D	2½	½	WBC 50, gold curve 0002422-200	Small granulomata seen micr. grossly normal	Normal
11	108221	24	W	D	2½	2½	WBC 650, neutrophils 65%, lymphos. 35%	Firm granular exudate about base	Normal
12	85443	22	W	D	4	1½	Normal (early in disease)	Sl. thickening at base	Mil. lesion in substantia nigra
13	98017	25	B	D	3½	3½	WBC 900, neutrophils 60%, lymphos. 40%, gold curve 555554300	Fibrinous and fibrinous adhesions about base	Extension from meninges into brain
14	95409	23	B	D	3	None	Clear at autopsy	Normal	In medulla is a single spherule surrounded by lymphos. and neutrophils
15	114420	21	B	D	3	None	No record	Normal	Mil. nodules scattered through cbr., medulla and cbl.

\* Army Institute of Pathology, Army Medical Museum, Washington, D. C.

† D = Disseminated.

characteristically found within the brain, and basilar meningitis is uncommon. The lesions of disseminated coccidioidomycosis are comparable to those of miliary tuberculosis, in which intracerebral granulomata are also very unusual. In fact, both the primary and the disseminated forms of coccidioidomycosis have much in common with the clinical picture and pathology of tuberculosis.<sup>15</sup> The miliary tubercle and caseous nodule of both diseases can be distinguished histologically only by discovery of the causative organism.

The case reported here is of interest for the unusually extensive intracerebral involvement following miliary spread of the organism.

**Case Report.\*** The patient was a male of Italian parentage, 21 years old at the time of his induction into the Army in November, 1942. The family and early personal histories are essentially negative. From April to September, 1943 he was in the Arizona desert, 100 miles west of Phoenix. During June and July he went on maneuvers for 3 weeks in the desert regions of southern California. About September 1 he developed pain in his chest and a dry non-productive cough which later was associated with expectoration of sticky colorless mucus. At about this time the patient first noticed a small papule behind his right ear. The lesion slowly increased to 1 cm. in diameter while the surface became ulcerated and discharged pus. Early in October he began having frequent drenching night sweats, not accompanied by any marked loss in weight.

On October 20, 1943, he was admitted to a station hospital where the granulomatous lesion behind the right ear was noted, as well as an enlargement of the adjoining cervical lymph nodes and bilateral supraclavicular lymphadenopathy. A Roentgen ray of the chest showed clear lung fields and widening of the mediastinum. Microscopic examination of the sputum and of the pus from the skin lesion revealed the spherules of *Coccidioides immitis*. Skin tests with coccidioidin were negative in dilutions of 1:1000 and 1:100. This is a not infrequent finding in disseminated coccidioidomycosis,<sup>13</sup> in contrast to the positive reactions almost invariably found accompanying the primary pulmonary lesion. The serum complement-fixation test was positive (Stanford University School of Medicine) in a titer of 1:64. This was interpreted by Dr. C. E. Smith as evidence of dissemination.

When admitted to this general hospital in November, 1943 the patient still appeared well nourished and complained only of cough, occasional blurring of vision, and a feeling of weakness. However, he had a daily rise in temperature to 101° F. and his general condition gradually declined. During the course of his illness many scattered granulomata appeared on the skin. These usually drained for several weeks but eventually healed. Lymphadenopathy often ended in abscess formation, the spherules of *C. immitis* being recovered from the pus.

Early in January, 1944 headache, of which he had previously rarely complained, became persistent and was associated with progressive amblyopia and diplopia. In May the signs and symptoms of bilateral III nerve paralysis were more pronounced and were accompanied by loss of the power of accommodation. At this time vomiting also set in and he became quite drowsy, though it was possible to rouse him. By the end of June this had deepened into stupor and for weeks before death on July 24, 1944, he was comatose.

**Laboratory Findings.** On admission the red cell count was 4,590,000, hemoglobin 90%, leukocytes 15,300 (neutrophils 70%, lymphocytes 16%, eosinophils 3%, basophils 2%). Before death the number of erythrocytes fell to 3,000,000, leukocytes to 13,000. Spherules of *C. immitis* were frequently found in the sputum. The urinary findings were not significant. The Kahn and Wassermann tests were negative; the complement-fixation test for coccidioidal infection remained at the high titer of 1:64. Spinal fluid (1/18): leukocytes 0,

\* Clinical data were made available through the courtesy of Major Arthur Heyman.

globulin 1+, colloidal gold curve 5543210000, no organisms. 6/25: leukocytes 120 (neutrophils 15%, lymphocytes 85%), globulin 4+, colloidal gold curve 5555555321, no organisms. Biopsy of the skin lesion showed a typical granuloma with foreign body giant cells containing the spherules of *C. immitis*.

*Roentgen ray.* The admission film showed a mass in the superior mediastinum, most pronounced on the right; the lung fields were clear. Subsequent chest films revealed a slight increase in width of the mediastinum. Skull, long bones, and pelvis were negative.

*Therapy.* While at the station hospital the patient received 2 immunotransfusions of blood from donors who had recovered from coccidioidomycosis. There was no evidence of any beneficial effect. Goldstein and McDonald<sup>8</sup> used this treatment in 2 patients who were critically ill with pulmonary consolidation and effusion due to infection with *C. immitis* and both showed immediate clinical improvement.

At this hospital, potassium iodide was administered, beginning with 10 minims t.i.d. The amount was gradually increased to 60 minims t.i.d. and was continued for 2 months without evidence of improvement. Intravenous injections of coccidioidal vaccine were given on alternate days beginning with 0.1 cc. of a 1:1000 dilution and increasing to 2 cc. of the undiluted vaccine. This amount was administered for 2 months, but no improvement was noted.

Two courses of penicillin therapy were given. During the first, from March 17 to April 11, 3,120,000 Oxford units were administered intramuscularly in quantities of 15,000 units every 3 hours. In the second course, from May 22 to June 21, a total of 3,720,000 Oxford units were similarly injected. Although the skin lesions appeared smaller, this was due to disappearance of the secondary hemolytic staphylococcal infection, rather than to any effect upon the fungus. The failure on the part of penicillin to inhibit the growth of *C. immitis* is in striking contrast to the results obtained with 3 cases of actinomycosis of the jaw treated in this hospital. After 3 to 4 weeks of penicillin therapy the lesions healed and have remained so without recurrence for periods of 7 months to a year.

*Autopsy.* The body was that of an emaciated 22 year old white male. Near the base of the neck on the right side were 2 shallow ulcerations each 1.5 cm. in length. Behind the left ear and on the left side of the neck were similar lesions covered by a thin crust and measuring 3 mm. in diameter. The first interphalangeal joint of the right middle finger was swollen and fluctuant. Axillary lymphadenopathy was most marked on the right. Beneath the right pectoral muscles was an irregular 3 x 5 x 7 cm. abscess cavity filled with viscid yellow-brown pus, which on culture yielded a pure growth of *C. immitis*.

The peritoneum was thin and glistening, no free fluid was present, and the normal visceral relations were preserved. The serosal surfaces of the pericardium were smooth, the sac contained 10 cc. of clear yellow fluid. The pleuræ were transparent, no adhesions or free fluid were present. The mediastinal and hilar lymph nodes were enlarged, matted together, and on section had a speckled appearance due to many orange-yellow areas of focal necrosis. The para-aortic and mesenteric lymph nodes were likewise enlarged, some reaching a length of 2 cm. Histologically, they had lost all trace of their normal architecture. Small islands of lymphoid tissue were scattered through masses of granular pink staining material containing the spherules of *C. immitis* in large numbers.

The lungs were grossly normal. Microscopic examination revealed several small collections of lymphocytes and multinucleate foreign body giant cells. Only rarely was a spherule of *C. immitis* seen in these lesions, although in the adjacent lymph node they were very numerous. Many of the bronchioles were filled with neutrophils, others contained necrotic material in which were many spherules.

The heart weighed 280 gm.; gross and microscopic examination failed to reveal any abnormalities. The spleen, which weighed 140 gm., was likewise

grossly normal. Histologically, there were several miliary tubercles, though no spherules could be found.

The entire gastro-intestinal tract, including the liver, gall bladder, and pancreas, was grossly normal. Only in the liver did histologic examination show occasional scattered coccidioidal granulomata.

Both kidneys were of normal size, shape, and consistency. The capsule stripped with some difficulty, although the underlying surface was smooth, dark red in color. On the surface of the left kidney was an irregular, poorly defined, yellow-white discoloration which on section was seen to extend a short distance into the cortex. The majority of the papillæ in each kidney bore irregular partly confluent 2 mm. areas of caseation necrosis. Microscopically, the glomeruli and tubular epithelium were intact. Scattered through the parenchyma of both cortex and medulla were numerous granulomata consisting of epithelioid cells, lymphocytes, plasma cells, and occasional foreign body giant cells some of which contained the spherules of *C. immitis*. The ureters, bladder, prostate, and testes were normal.

The left adrenal appeared normal; but the right was greatly enlarged, measuring 5 x 4 x 3 cm. On section a firm yellow-white mass was seen replacing most of the medulla. Histologically both cortex and medulla were found to be involved; much of the normal tissue was destroyed and replaced by a pink staining granular material containing countless spherules of *C. immitis*. About the margins of the necrotic areas were foci of granulation tissue.

The brain weighed 1580 gm., the convolutions were of normal complexity though somewhat flattened. About the base, and most dense at the optic chiasm, was a firm, gray, translucent exudate. Section through the midbrain revealed a central, 1.5 cm. spherical yellow-green mass replacing the normal tissue (Fig. 1). It extended posteriorly to involve the cephalic portion of the pons, and anteriorly into the mesencephalon where it infiltrated the tegmentum and pulvinar on the left. The cerebral aqueduct was not compressed. At the level of the optic chiasm the meningeal exudate infiltrated the nervous tissue about both optic tracts and extended into the hypothalamus. A firm 1.5 cm. nodule was present on the floor of the left lateral ventricle in the region of the caudate nucleus. Similar lesions averaging 5 mm. in diameter were scattered through the cortical and subcortical areas of the parietal and temporal lobes. In the right cerebellar hemisphere at the cortico-medullary junction were 2 discrete 1.3 cm. gray-green nodules (Fig. 2). A similar lesion, 5 mm. in diameter, was present in the left cerebellar hemisphere.

On histologic examination, many granulomata containing spherules of *C. immitis* were found in the subarachnoid space. In several areas the underlying cerebral cortex had been invaded by direct extension. However, the lesions of the cerebellum, the mid-brain, the lateral ventricle, and the smaller foci scattered through the cerebral hemispheres (Fig. 3), were apparently due to hematogenous distribution of the fungus.

In whatever tissues they were found, the spherules of *C. immitis* were surrounded by granulation tissue which closely resembled that seen in tuberculosis. The organisms averaged 20 to 30 micra in diameter, though when recently liberated as endospores they were only 3 micra in width. The wall, which was about 1 micron thick, consisted of two layers—an inner one that stained with eosin, and an outer highly refractile colorless membrane. The content of the spherules was basophilic and often vacuolated. Many were empty; in others the inner mass was subdivided into smaller bodies which, in the more mature stages, had rounded up to form the characteristic endospores. No mycelial threads were seen.

**Cultural Studies.** The spherules found in the sputum, pus, or tissues of the infected man or animal are generally thought to represent the parasitic phase in the life cycle of *C. immitis*. This phase consists in the growth of the spherule and the maturation of its endospores. The spherule finally ruptures and the endospores pass into the tissues, there in turn to become spherules and liberate a new generation of endospores. When spherules are placed on culture media, hyphæ grow out from them to form a mycelium in which some of the cells

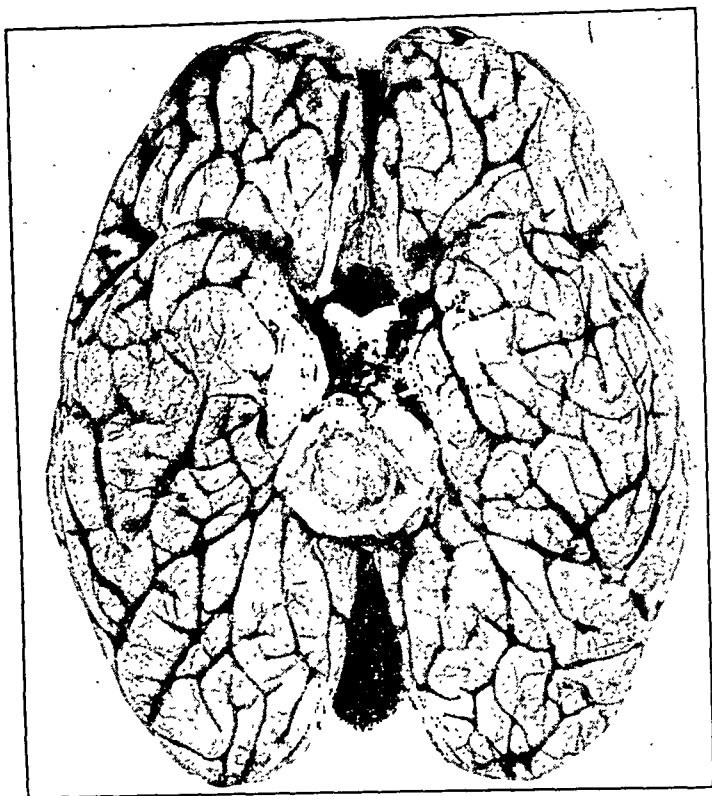


FIG. 1.—Ventral surface of brain. The cerebellum has been removed, the section passes through the midbrain just anterior to the pons. In the center of the cut surface is a circular 1.5 cm. granuloma. About the optic chiasm is a heavy gray translucent exudate.

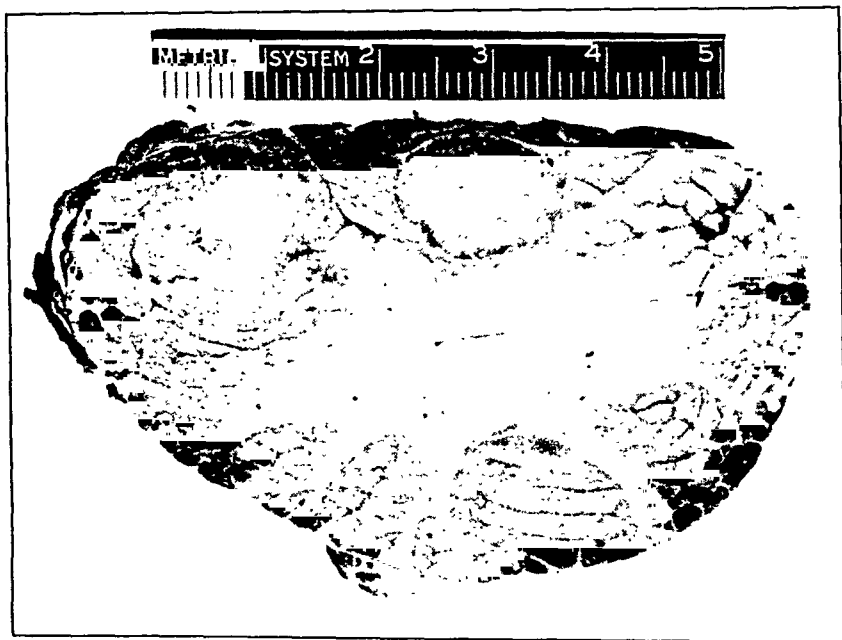


FIG. 2.—Vertical section through the right cerebellar hemisphere. At the cortico-medullary junction of the ventral aspect are two circular granulomata. One of these is well circumscribed, the other is infiltrating the surrounding tissue.



enlarge to form reproductive bodies known as chlamydospores. Until recently, spherule formation had not been observed in this; the so-called saprophytic phase of the life cycle of the fungus.

In 1914, MacNeal and Taylor<sup>10</sup> inoculated fresh pus into tall tubes of ascitic fluid or gelatinized horse serum containing a piece of sterile rabbit kidney. A mycelium did not develop when these tubes were kept in an atmosphere of hydrogen, but the spherules originally present in the pus continued to multiply, occasionally for as long as 3 weeks. Lack,<sup>9</sup> in 1938, used Hall tubes which he filled with neutral glucose broth to well above the point of constriction. The inoculum of chlamydospores suspended in egg albumen was pipetted into the tube and the constriction sealed off with a sterile marble. Gentle heating then partly coagulated the medium. Spherules appeared after about 7 days; the growth of hyphae was completely inhibited.

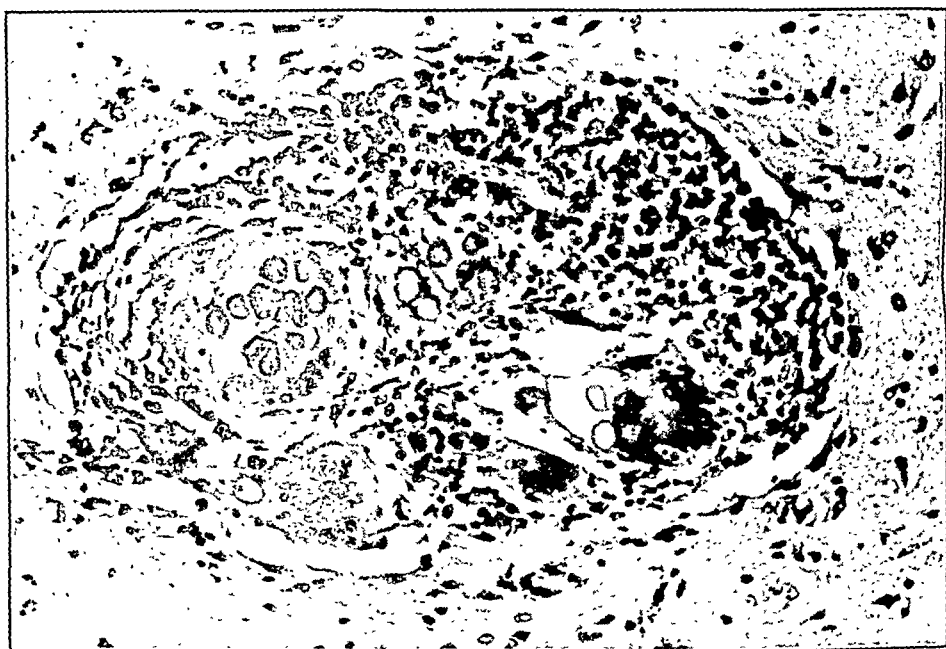


FIG. 3.—Miliary granuloma in the cerebral cortex. Four large foreign body giant cells are at the periphery, 3 contain spherules of *C. immitis*. Several spherules are present in the center of the lesion. The small cells are lymphocytes and plasma cells. (Hematox. eos.  $\times 330$ .) (U. S. A. Med. Mus. Neg. No. 81998.)

In these investigations spherule formation occurred under conditions simulating those found in the animal body, and a mycelium failed to develop. They thus supported the view that the parasitic and saprophytic phases of the life cycle were separate and distinct. However, in 1941, Baker and Mrak<sup>2</sup> reported finding structures resembling spherules in 3 of 16 strains of old partially dried out agar cultures of *C. immitis*. Culture spherules were found after 1½ to 2 months incubation, when active growth of the fungus had ceased. They were never seen in liquid media. In a subsequent article<sup>3</sup> these authors point out that the discovery of spherules in cultures eliminates the need for postulating two independent phases in the life cycle of *C. immitis*. They state further that thus far culture spherules had been observed in only 4 strains, and constantly in only 1. It seemed desirable, therefore, to attempt the production of both mycelium and spherules in the same culture by somewhat different methods.

**Technique.** Sputum and pus obtained from this case were streaked on Sabouraud's agar and kept at room temperature. Mycelial growth in the form

of a loose, white, whorled cotton-like fluff appeared in all tubes after 5 days. Two weeks after inoculation many hyphæ had grown over the inner surface of the tube where no agar was present, facilitating microscopic examination. In some of these regions rectangular chlamydospores were found; spherules were never seen. Subcultures were made to agar plates for the purpose of studying colony formation (Fig. 4) and to eliminate any spherules that had been carried over in the original inoculum which might still be present in the culture.

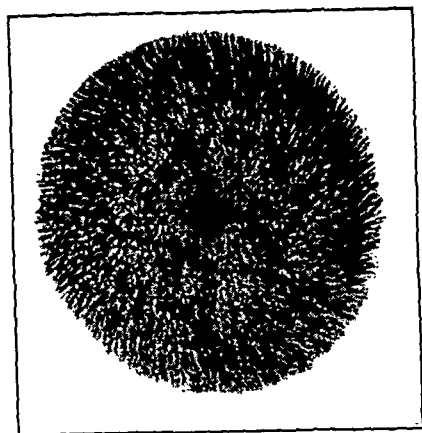


FIG. 4.—Mycelium of *C. immitis* 6 days after inoculation on Sabouraud's agar.



FIG. 5.—Growth of mycelium and spherules in citrated human blood kept in roller tube. The spherules are enmeshed in the mycelium which is obscured by erythrocytes. (Fresh preparation.  $\times 80$ .)

Six or 7 days after subculture, bits of the mycelium were inoculated into test tubes containing 1.5 cc. of heparinized or citrated blood kept at  $37.5^{\circ}\text{C}$ . The tubes were placed in the roller tube apparatus designed by Gey and modified by Coman and Stabler<sup>4</sup> for use in tissue culture. Essentially this is a slowly revolving (9 r.p.h.) circular rack that carries about 50 tubes which lie on their sides, but are slightly tilted so that none of the blood will come in contact with the rubber stopper. The fungus grows on the inner surface of the tubes where it is bathed by the slowly circulating blood. If a tube is placed on the upward tilted stage of a microscope, and its bottom directed toward the observer, the blood will collect there, permitting examination of the fungus attached to the sides of the tube.

**Experimental Observations.** Twenty-four hours after inoculation, microscopic examination showed small islands of mycelium scattered over the inner surface of the tubes. During the next 3 days the colonies slowly increased

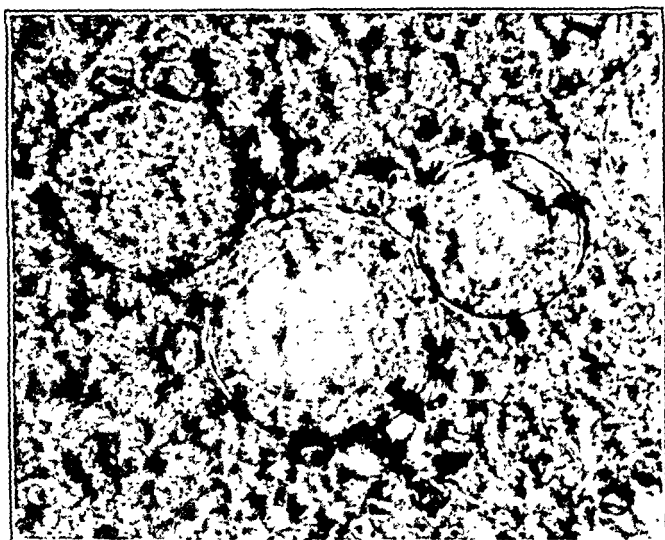


FIG. 6.—Three large spherules, 50 to 60 micra in diameter, growing in citrated blood within a roller tube. In 2 the cytoplasm surrounds a large central vacuole, in the third it completely fills the spherule. (Fresh preparation.  $\times 450$ .)

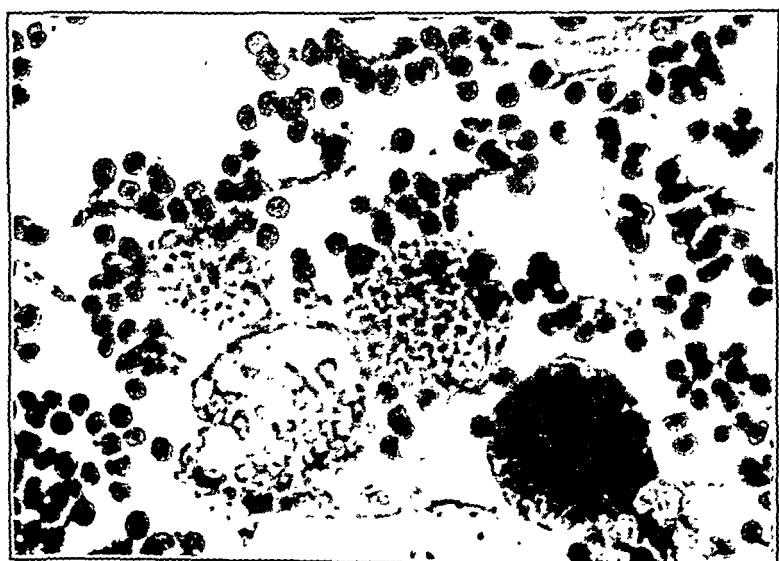


FIG. 7.—Section of mycelial mat grown in roller tube, showing 4 poorly defined spherules with their endospores. One spherule is almost empty, but still contains a few large endospores some of which are passing through a rent in the wall. The solid black disks scattered through the field are erythrocytes. (Hematox. eos.  $\times 810$ .) (U. S. A. Med. Mus. Neg. No. 82000.)

in size, and spherules began to appear. These were often embedded in a mass of hyphae (Fig. 5), but occasionally were wholly free of the mycelium. In some instances the cytoplasm formed a peripheral layer beneath the highly

refractile wall of the spherule and surrounded a large central vacuole (Fig. 6). When spherules were isolated and placed in a hanging drop of lactose broth, hyphæ grew from the endospores within 24 hours. Rarely this type of germination was also seen within the blood tubes. Though never observed in the living state, histologic sections of the mycelial mats removed from the tubes showed large endospores within and surrounding collapsed spherules (Fig. 7). This would indicate that spherule formation by the liberation of endospores was taking place.

Four to 5 days after inoculation, chlamydospores began to appear as localized swellings on the hyphæ. Some remained small and fusiform, others formed spherical structures which might be mistaken for culture spherules. However, the absence of endospores in the former and their presence in the latter is an aid to identification. Culture spherules in which no cleavage has taken place have a granular cytoplasm; that of chlamydospores is usually clear and almost hyaline. The development of spherules from chlamydospores noted by Lack<sup>9</sup> was not seen in these cultures, but its occurrence is not improbable. Degenerative changes began 10 to 14 days after inoculation. The cells of the mycelium became vacuolated, the hyphæ broke up into short lengths, the spherules disintegrated and disappeared.

Replacing air in the tubes with hydrogen had no apparent effect upon the development of the mycelium or spherules. Nor was growth altered by the kind of anticoagulant used, both heparinized and citrated blood proving satisfactory. If the tubes were placed on a slant, but not rotated, the erythrocytes settled out; some mycelial growth took place, but spherules were rarely found. To test the effect of rotation alone, brain heart infusion broth instead of blood was used. A mycelium formed, but no spherules developed. In serum a good growth of mycelium occurred with the production of many chlamydospores and a moderate number of spherules.

**ANIMAL INOCULATION.** Mycelium growing on Sabouraud's agar was suspended in 0.85% sodium chloride; 0.5 cc. was injected intraperitoneally into 4 mice, 2 hamsters, and 4 frogs. In 2 additional frogs, bits of mycelium were placed in the anterior chamber of one eye.

*Mice.* The mice, serving as a control series for the hamsters and frogs, were killed at intervals between 10 and 32 days after inoculation. In all, the spleen and mesenteric lymph nodes were moderately enlarged. Several 1 mm. yellow-white nodules were scattered through the liver and both lungs. Histologic examination showed the characteristic granuloma containing many spherules of *C. immitis*.

*Hamsters.* The first animal died 10 days after inoculation, the second was killed on the following day. The lungs were riddled with confluent 1 to 3 mm. white nodules (Fig. 8). Similar lesions, but more discrete, were present in the liver and spleen. The mesenteric lymph nodes were enlarged and matted together. Microscopically the typical granulomata consisting of lymphocytes, epithelioid cells, and foreign body giant cells were seen. The spherules were often very large; occasionally one was found that had ruptured, the liberated endospores infiltrating the surrounding tissue (Fig. 9). In view of the presence of coccidioidomycosis in wild rodents of regions in which the disease is endemic,<sup>16</sup> the susceptibility of the hamster to the fungus was not unexpected.

*Frogs.* These animals were inoculated to determine if the fungus when introduced into a cold blooded animal would grow, and if it did, whether as a mycelium or by endosporulation. The first frog died 3 days after inoculation. Death was due to an intercurrent infection, the so-called "red leg." Flakes of fibrinous exudate were attached to the surface of the bladder, stomach, spleen, and liver. Histologically the lesions consisted of fibrin, enmeshed in which were many eosinophils, basophils, and lymphocytes. Scattered among them were many short hyphal fragments, the cells of some of which had rounded up to form small spherical chlamydospores.

A second frog was killed 8 days after inoculation. On the peritoneal surface near the site of inoculation were two yellow-white nodules, each 2 mm. in diameter. A 2.5 mm. nodule was present in the region of the pancreas, and

two smaller ones were on the surface of the bladder. Many 0.3 mm. tubercles were found in the mesentery. Histologically the lesions consisted of connective tissue infiltrated by many eosinophils, macrophages, and lymphocytes. Many small spherules, most of which showed only a single cleavage plane, were found within the cytoplasm of the macrophages. Occasionally one or two cell

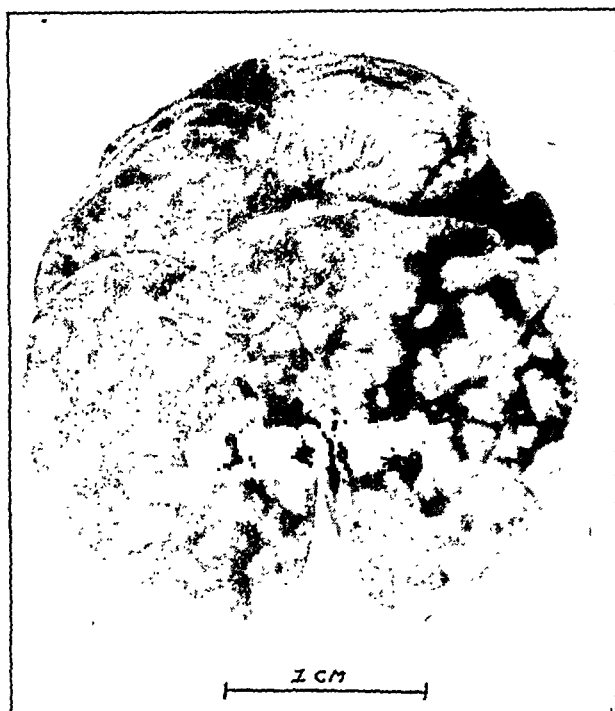


FIG. 8.—Heart and lungs of a hamster that died 10 days after intraperitoneal inoculation with the mycelium of *C. immitis*.

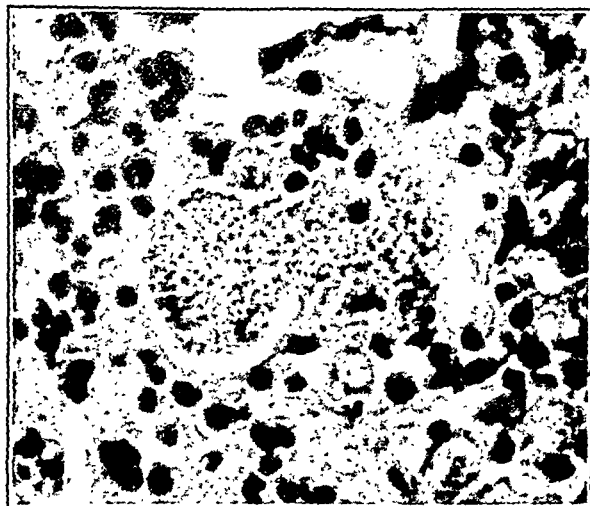


FIG. 9.—Section of the spleen of hamster shown in previous figure. A large spherule has ruptured and the endospores are escaping into the adjacent tissue. (Hematox. eos.  $\times 450$ .)

lengths of degenerating mycelium were also found; most had been phagocytized. Foreign body giant cells were almost wholly absent. When bits of the tissue were placed on Sabouraud's agar, growth of the fungus was apparent after 2 days. The remaining animals were killed 18 days after inoculation. In both only a few 0.1 mm. fibrous granules were found on the peritoneum near the site of injection.

To enhance the possibility of hyphal growth, bits of mycelium were placed in the anterior chamber of one eye in each of 2 frogs. After 2 weeks the cornea was hazy, but the mycelium had disappeared. Histologically, small granulomata were found in the cornea and iris similar to those seen on the peritoneal surfaces of the other animals. There had been no growth of the mycelium.

**Discussion.** The course of the patient's illness was quite typical of that usually seen in disseminated coccidioidomycosis. The onset of symptoms with cough indicates that the primary lesion was in the lungs. Yet, though spherules of *C. immitis* were often found in the sputum, the lung fields were clear on Roentgen ray, and gross lesions were not found at autopsy. Mediastinal lymphadenopathy associated with minimal pulmonary involvement, as demonstrated in this case, is a frequent finding in the generalized disease.

The first evidence of an intracranial lesion was occasional blurring of vision noted by the patient 8 months before death. His ability to survive for so long after involvement of the central nervous system probably accounts for the massive character of the lesion found there. However, even shortly before death the fungus could not be isolated from the spinal fluid. This is also true of the 15 cases listed in Table 1.

The presence of numerous spherules in association with an actively growing mycelium in the roller tubes lends support to the contention of Baker and Mrak that the parasitic and saprophytic life cycles of *C. immitis* are not wholly separate and distinct; that they may occasionally occur simultaneously. A marked difference in these two phases of the life cycle of a number of pathogenic fungi has long been recognized. Using the roller tube technique and heparinized blood as a culture medium, one of these, namely *Histoplasma capsulatum*, was studied along with *C. immitis*. Here also both the mycelium and yeast-like form grew in the same culture tube.

Since it was now possible to grow the mycelium and spherules of *C. immitis* in the same culture as saprophytes, the next step would be to find both in animals as parasites. The hamster proved very susceptible to infection with the fungus, but only spherules were found in the lesions. Frogs were used in the hope that these animals, with their lower body temperature, would provide a more favorable environment for the mycelium, particularly if the latter were placed in the anterior chamber of an eye. However, no growth of the mycelium occurred and the spherules that developed only reached the two-cell stage. The granulomata found in the peritoneum and cornea were in the nature of a non-specific foreign body reaction.

**Summary.** A fatal case of disseminated coccidioidomycosis is reported in which the outstanding lesions were found in the brain. Fifteen additional examples of intracranial infection by the fungus are listed. The organism was isolated and both mycelium and spherules

grown in culture using the roller tube apparatus of Gey. Hamsters were very susceptible to the fungus, frogs were refractory. Neither in the patient nor in the experimental animals was there evidence of mycelial growth.

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## PNEUMOCOCCIC PNEUMONIA RESEMBLING PRIMARY ATYPICAL PNEUMONIA

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DURING the past few years much emphasis has been placed both by clinicians and laboratory workers on "primary atypical pneumonia, etiology unknown." This designation was suggested by the Commission on Pneumonia†<sup>7</sup> in place of the variety of terms that have been applied to this clinical syndrome. Many agents have been suggested as playing a rôle in its etiology. Clinical similarity to the proved virus pneumonias of the ornithosis group, epidemiologic studies, the negative bacteriologic results and the resistance to sulfonamide treatment have greatly contributed to the concept that this disease is due to a virus infection. However, it has been repeatedly stressed<sup>4,5</sup> that pneumonias of non-viral origin, such as coccidioidomycosis,<sup>2</sup> Q-fever,<sup>1</sup> and so on, can give a very similar clinical picture.§

Study of patients admitted to the Pneumonia Service of Harlem Hospital has impressed us with the not infrequent occurrence of cases of proved pneumococcic pneumonia with a picture closely resembling

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† A Board for the investigation and control of influenza and other epidemic diseases in the United States Army.

§ Dr. H. A. Reimann has recently suggested that these be called "viroid" pneumonias. As he suggests, there is ample precedent for such a word, which also can better cope with atypical instances than could "atypical atypical pneumonia."—EDITOR.

primary atypical pneumonia. The insidious onset, patchy infiltration of the lung, scanty sputum with a hacking cough, relative bradycardia together with the Roentgen ray findings, have often led us to a tentative diagnosis of primary atypical pneumonia. The occurrence of positive blood cultures or the occasional appearance of complications such as a pneumococcic empyema, has made us more cautious in our clinical diagnosis of sporadic cases of primary atypical pneumonia. It is quite possible that the pneumococcic pneumonia may have been superimposed on a primary virus infection. However, the striking response in these patients to specific serum therapy and the increasing occurrence of sulfonamide-fast strains warranted further investigation.

In this paper, a study of cases of pneumococcic pneumonia in adults admitted to Harlem Hospital during the 4-year period (1939 to 1943) is reported, with special reference to atypical forms and their response to chemotherapy and specific serum treatment.

**Method.** The procedure adhered to by the Pneumonia Service at Harlem Hospital, in arriving at an etiologic diagnosis and the selection of proper therapy was as follows:

Immediately following admission, a complete history was obtained and physical examination carried out. Sputum was collected for typing and blood drawn for culture and initial immunologic studies (type specific agglutinins, precipitins and C-reactive protein). A Roentgen ray of the chest was taken as a routine. The patient was given chemotherapy as soon as the diagnosis of pneumonia was made. (Sulfadiazine, 4 gm. stat. and 1 gm. every 4 hours.)

Sputum was typed directly by the Neufeld method and after intraperitoneal mouse inoculation. Intraperitoneal fluid as well as mouse brain cultures were studied within the next 24 hours. If pathogenic organisms were not found, additional samples of sputum were examined.

The patient with characteristic pneumococcic pneumonia usually showed a response to chemotherapy by the time the sputum was typed. In the event that a response did not occur, despite an effective blood sulfonamide concentration, the isolated organisms were tested *in vitro* for fastness, and the patient's serum tested for sulfonamide inhibitors according to the method of MacLeod.<sup>6</sup> If the organism was fast to all of the sulfonamides and the patient still failed to respond, serum therapy was instituted promptly.

In some patients repeated examination of the sputum yielded no suspected pathogens. Under these circumstances another procedure was employed in an attempt to obtain a bacteriologic diagnosis. For this purpose a method which we have termed "reverse" typing was used. A sample of serum was obtained from the patient every 2nd day and was tested against 56 stock strains of pneumococci for "quellung" reaction. In the average case of pneumococcic pneumonia, after 5 to 7 days the patient had developed a sufficiently high concentration of antibodies to produce distinct capsular swelling with the homologous type pneumococcus. Details of the procedure are reported elsewhere.<sup>10</sup>

**Case Reports.** Some illustrative cases are here reported.

**CASE 1.** *Atypical pneumococcic pneumonia without response to chemotherapy.*

H. S., aged 42, was admitted with a 3-day history of cough, fever, chills, night sweats and pain in the left chest. The temperature was 104° F., with a relative bradycardia throughout the course. The W.B.C. on admission was 2150 and 1 week later 16,750. There was slight dullness with râles over the right lower lobe. Serial Roentgen rays revealed migrating pneumonia involving right lower lobe, right middle lobe and then the left lower lobe. Type XII



pneumococcus was found in the sputum, mouse peritoneal fluid and mouse brain. Test for C-reactive protein was positive and agglutinins for Type XII appeared in rising titer during the course. The temperature was spiking for 4½ weeks in spite of 2 courses of sulfonamide therapy. There was no evidence of complications. There was a return to normal by lysis and the patient was discharged after 5 weeks, asymptomatic.

*Comment.* This case is cited as a suggestive example of a primary virus infection followed by a secondary invasion by a bacterial organism. The patchy migrating pneumonia, the relative bradycardia, leukopenia and the lack of response to chemotherapy resemble the picture seen in primary atypical pneumonia. The secondary rise in leukocytes with the appearance of specific antibodies indicate that pneumococcus XII was a secondary invader. As pointed out later, we and others have observed repeatedly the ineffectiveness of sulfonamides and the apparent superiority of specific serum therapy in treating infections caused by this type of pneumococcus. (See Table 2.) The prolonged course as seen in this patient occurs often in cases with migrating and bilateral pneumonia, although in our experience; this is very rare in pneumococcus Type XII pneumonia.\* (See Table 1.)

*CASE 2. Atypical pneumococcic pneumonia with response to chemotherapy.*

J. P., aged 55, was admitted with a history of insidious onset of cough, substernal ache, fever and chills. The temperature was 103° F. with a relative bradycardia. There was slight dullness with numerous fine râles over both lower lobes. Roentgen ray revealed bilateral infiltration of the lower lobes. The W.B.C. was 11,000. Type III pneumococcus was found in the sputum and mouse peritoneum. Positive agglutinins for Type III appeared irregularly. Sulfadiazine produced a response and then was discontinued. On the 12th day, the temperature rose to 102° F. and sulfadiazine was reinstituted with prompt response and recovery.

*Comment.* In our experience, patients with pneumonia caused by pneumococcus Type III have shown, frequently, absence of demonstrable antibodies from their serum. With daily examination, antibodies are found to appear and disappear from the blood stream, and can be easily missed if only a single examination is made. The presence of large numbers of pneumococcus Type III in the sputum and the response to sulfonamide therapy indicate that Type III was etiologic in this case. Not infrequently, relatively large amounts of free SSS III can be found in the serum in the early stages of the disease, which establishes the etiology and at the same time may partially explain the lack of demonstrable antibodies.

*CASE 3. Atypical pneumococcic pneumonia with response to serum.*

E. W., aged 80, was admitted with a 2-week history of cough, headache, chilly sensations and fever. The temperature was 102° F. with a relative bradycardia. There was diminution of breath sounds with râles in both lower lobes. Roentgen ray examination revealed patchy infiltration of both lower lobes. Type XVIII pneumococcus was found in the sputum, mouse peritoneum and mouse brain cultures. On the 2nd day of hospitalization, the temperature was 104.2° F. Rabbit serum (Lederle), Type XVIII (142,500 units) was given. The patient recovered.

*Comment.* This patient presented a picture characteristic of primary atypical pneumonia. The patient's niece, however, was ill at the same time with classical pneumococcic pneumonia caused by the same type of pneumococcus. The patient's response to serum therapy was no less striking than the effectiveness of the sulfonamide therapy in the niece.

*CASE 4. Atypical pneumococcic pneumonia with high titer of cold hemagglutinins.*

S. J., a 30 year old colored male was admitted to the hospital with a temperature of 102° F., pulse 92, respiration 16. He gave a history of chilly sensations with non-productive cough the day before admission. He did not

\* This case was admitted to Harlem Hospital after March 1, 1943, and is not included in Tables 1 and 2.

appear acutely ill. Physical examination revealed râles over the left lower chest with no signs of consolidation. The Roentgen ray department reported bronchopneumonia in the left lower lobe. Next morning his temperature rose to 103.4° F. and continued to spike between 101° and 104° F. There was marked relative bradycardia throughout the period of 9 days of high temperature. The W.B.C. was 7950. A Type XXI pneumococcus was recovered from the sputum. Sulfadiazine (23 gm.) was ineffective. During the first 10 days of the disease there were no agglutinins in the patient's serum for Type XXI pneumococcus. Then the type specific agglutinins appeared and rose to a titer of 1:64 (2+) 2 weeks after onset of the disease. Cold agglutinins which were absent at the onset appeared on the 7th day and rose to a titer of 1:2000. Absorption of the Type XXI agglutinins by the homologous pneumococci did not change the titer for cold agglutinins in the serum.

CASE 5. *Atypical pneumococcic pneumonia with high titer of cold hemagglutinins.*

G. S., a 32 year old white male, gave a history of an upper respiratory infection for 2 weeks prior to admission. He was treated by his local physician for 5 days with sulfadiazine without response. The diagnosis at this time was pneumonia of the left lower lobe. The patient was restless, dyspneic and developed erythema over the abdomen. The sulfonamide was discontinued and the patient began to show some improvement. However, after a few days he started to cough again and was sent to the hospital. Roentgen ray on admission showed peribronchial infiltration in the left lower and right upper lobes. The temperature was 103° F.; pulse 100; respiration 32. Next morning his temperature went up to 105° F. and then gradually fell to normal after 7 days. Type XXXIII pneumococci were recovered from the sputum and a high titer of homologous agglutinins were found in his serum. At the same time cold agglutinins in a titer of 1:16,000 were present in the patient's serum.

*Comment* (Cases 4 and 5). In view of the report of cold agglutinins<sup>9</sup> in primary atypical pneumonia, these 2 cases are of special interest. Cold hemagglutinins are usually not found in pneumococcic pneumonia in high titers. Thomas *et al.*<sup>11</sup> have reported cold hemagglutinins in a large number of primary atypical pneumonias where simultaneously agglutinins for an indifferent streptococcus were found. They also observed the same titer of cold agglutinins after absorption of the streptococcic agglutinins from the convalescent serum.

**Collected Data.** In hospital and private practice, the Roentgen ray findings and failure to respond to chemotherapy have been most commonly used as the outstanding objective criteria in the diagnosis of sporadic cases of primary atypical pneumonia. To evaluate these 2 criteria, tables of their frequency in pneumococcic pneumonia were prepared. Table 1 represents the occurrence of bilateral patchy infiltration in pneumococcic pneumonia, and Table 2 the response to chemotherapy of pneumonia patients with either typical or atypical Roentgen ray findings. Most of the common pneumococcal types are represented. Some of the higher types were chosen at random.

*Comment on Table 1.* Bilateral patchy infiltration has been claimed to be one of the characteristic findings in primary atypical pneumonia. It can be seen from Table 1 that the incidence of bilateral involvement for most types is about 10%. These lesions usually were patchy, while the unilateral lesions were, in general, a dense lobar consolidation. Even in the latter group, however, a patchy bronchopneumonic infiltration was encountered in 25 to 30%. In view of the fact that more recently, in outbreaks of primary atypical pneumonia in Army camps, unilateral involvement of the lungs has been noted frequently,<sup>8</sup> the

differentiation by Roentgen ray between primary atypical pneumonia and pneumococcic pneumonia is made extremely difficult.

TABLE 1.—ROENTGEN RAY FINDINGS IN ADULT PNEUMONIA IN HARLEM HOSPITAL  
JULY 1, 1939 TO MARCH 1, 1943

Pneumococcus types	Roentgen Ray Findings		Total No. of cases	Type incidence in % of total
	Bilateral (%)	Unilateral (%)		
I . . . . .	10.5	89.5	239	17.1
II . . . . .	8.0	92.0	100	7.2
III . . . . .	14.0	86.0	272	19.5
VII . . . . .	5.7	94.3	279	20.0
VIII . . . . .	4.8	95.2	189	13.5
XII . . . . .	0.0	100.0	32	2.3
XIII . . . . .	9.1	90.9	22	1.6
XIV . . . . .	8.5	91.5	71	5.1
XV . . . . .	21.4	78.6	14	1.0
XIX . . . . .	5.3	94.7	75	5.3
XXV . . . . .	10.7	89.3	56	4.0
XXXIII . . . . .	10.4	89.6	48	3.4
Grand totals . . . . .	8.8	91.2	1397	100.0

TABLE 2.—RESPONSE TO SULFONAMIDE THERAPY IN ADULT PNEUMONIA PATIENTS IN  
HARLEM HOSPITAL, JULY 1, 1939 TO MARCH 1, 1943

Pneumo- coccus types	Roentgen ray findings					
	Bilateral			Unilateral		
	Total No. of cases*	Response in less than 48 hours (%)	No response in 48 hours (%)	Total No. of cases*	Response in less than 48 hours (%)	No response in 48 hours (%)
I . . . . .	10	50.0	50.0	125	63.2	36.8
II . . . . .	4	25.0	75.0	46	69.7	30.3
III . . . . .	21	28.5	71.5	143	60.1	39.9
VII . . . . .	12	33.3	66.7	156	59.6	40.4
VIII . . . . .	6	66.7	33.3	117	56.5	43.5
XII . . . . .	0	0	0	22	40.9	59.1
XIII . . . . .	2	50.0	50.0	18	66.7	33.3
XIV . . . . .	4	25.0	75.0	41	48.8	51.2
XV . . . . .	1	0	100.0	9	44.5	55.5
XIX . . . . .	3	33.3	66.7	60	31.6	68.4
XXV . . . . .	3	33.3	66.7	34	52.9	47.1
XXXIII . . . . .	4	50.0	50.0	30	66.6	33.4
No pathogens . . . . .	14	35.7	64.3	77	31.1	68.9
Total . . . . .	84	36.8	63.2	878	53.3	46.7

\* Deaths in less than 48 hours omitted.

*Comment on Table 2.* Response to chemotherapy has been designated as a fall in temperature within 48 hours, with subsequent recovery. The choice of 48 hours is purely arbitrary. A fall in temperature by lysis may also be due to chemotherapy, but this is difficult of interpretation. Therefore, this table does not necessarily represent the true and complete effectiveness of sulfonamide therapy.

Of patients with pneumonia due to the common as well as the higher types (except XII and XIX), with unilateral involvement, about 60% responded to chemotherapy within 48 hours. In the cases where no pathogens were found in the sputum, 30% responded in 48 hours. In the group with bilateral involvement the results are less favorable

for all types. Only about 35% of this group responded in 48 hours. The same incidence of response was found in the group where no pathogens were found in sputum. These figures indicate that a response to chemotherapy is not necessarily an important diagnostic aid in the differential diagnosis between pneumococcic pneumonia and primary atypical pneumonia.

**Discussion.** From the cases and tables presented above, it can be seen that not infrequently the pneumococcic pneumonias show features characteristic of primary atypical pneumonia. Among these are bilateral patchy infiltration (Table 1); failure to respond to chemotherapy (Table 2); presence of cold agglutinins (Cases 4 and 5); relative bradycardia (Cases 1, 2 and 3); spiking temperature (Case 3); normal leukocyte count or leukopenia (Cases 1 and 4); dry cough with scanty sputum; frontal headache, and so on.

Many investigators reporting cases of primary atypical pneumonia have found higher types of pneumococci in the sputum of their patients. Some have regarded these higher types as possible secondary invaders to a primary viral infection, but they have been disregarded by most investigators. The occurrence of positive blood cultures reported in pneumonia caused by the higher types (10 to 15%), the appearance of agglutinins in rising titer, the isolation of organisms from chest fluids, lung suction and autopsies, and the response to serum therapy,<sup>3</sup> however, stamp these higher types as active invaders.

Recently, Thomas *et al.*<sup>11</sup> have isolated an indifferent streptococcus from the lungs of a fatal case of primary atypical pneumonia. The convalescent serum obtained from 55 of their 101 cases of atypical pneumonia gave positive agglutination reactions with this streptococcus. These authors have also obtained similar strains of indifferent streptococcus from other fatal cases. The rôle of this organism as possible primary or secondary invader has not been established as yet. In cases where no pathogens are found in the sputum, the possibility of a bacterial invader cannot be ruled out on this observation alone. It is generally accepted that in tuberculosis the finding of acid-fast organisms in sputum is dependent on the type of lesion and on a free communication between the lesion and a bronchus. Negative sputum findings in miliary tuberculosis of the lung is common experience. A similar mechanism may play a rôle in the failure to isolate pneumococci from cases of pneumococcic pneumonia.\* Recently 8 out of 20 cases of this group were "typed" for pneumococci by the "reverse" typing method.<sup>10</sup>

There are cases which resemble the primary atypical pneumonias clinically and respond well to chemotherapy. Worthy of note is the "no pathogens in sputum" group in which 33% of the cases responded within 48 hours. On the other hand, 40% of the pneumococcic pneumonias failed to respond within 48 hours. Many cases of Types XII, XIX and III may be cited as examples (Table 2). On several occasions,

\* From the data of lung suction done previously at Harlem Hospital, it was found that in about 6% of the cases the etiologic organism was found in the lesion and not in the sputum.

however, infections caused by these types have responded well to serum therapy.\*

It is difficult to estimate the incidence of atypical forms in patients with pneumococcic pneumonia. If one accepts as the main criteria of atypical pneumonia a patchy, bronchopneumonic infiltration of the lungs and failure to respond to chemotherapy, then the incidence of atypical cases of pneumococcic pneumonia is about 20%.

It appears, therefore, that a differentiation between primary atypical pneumonia and pneumococcic pneumonia on the basis of clinical findings alone, is difficult. It is recommended that every effort be made in cases of primary atypical pneumonia, particularly where its occurrence is sporadic, to rule out the pneumococcus as a possible etiologic agent or as secondary invader, before denying the patient sulfonamide or serum therapy.

It is hoped that the wider use of penicillin for the treatment of pneumonic cases will afford an additional useful criterion for the differentiation of pneumococcic pneumonia and primary atypical pneumonia.

**Summary.** 1. The similarity between sporadic cases of primary atypical pneumonia and pneumococcic pneumonia has been illustrated by presentation of 5 representative case reports as well as data obtained from the study of large series of cases.

2. The Roentgen ray findings and lack of response to chemotherapy were not found to be of significant value in the diagnosis of sporadic cases of primary atypical pneumonia.

3. "Reverse" typing as an aid in diagnosis of pneumococcic pneumonia is suggested.

4. Of patients with pneumonia from whom no pathogenic bacteria were isolated from sputum, 33% responded to sulfonamide therapy within 48 hours.

5. Clinically, differentiation between atypical pneumococcic pneumonia and primary atypical pneumonia may be difficult. A bacteriologic etiology should be carefully ruled out before denying the patient chemotherapy or specific serum treatment.

We wish to express our gratitude to Dr. Colin M. MacLeod of New York University for his advice and criticism in the preparation of this manuscript.

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\* From a table published by Finland,<sup>3</sup> a similar conclusion can be drawn. For example, 27.7% of his Type XII pneumococcus cases which received no treatment, 12.7% which received chemotherapy, and only 2.5% which received serum, died. This holds also to a lesser extent, for Types XX, XXV and XXVII pneumococcic pneumonia.

## ROENTGEN THERAPY OF BOECK'S SARCOID

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*Pathology and Diagnosis.* The cause of sarcoid and its relationship to tuberculosis are matters that remain in dispute. Schaumann, who is given credit for establishing the relationship of many of the clinical entities that now are recognized as a feature of this disease, regarded it as an atypical form of tuberculosis, but others have taken issue with this view.<sup>2</sup> Recent studies indicate that the lesions of sarcoid may involve practically every organ or system in the body, but show a predilection for the lymph nodes and other structures of the reticulo-endothelial system.<sup>11</sup> Regardless of location the histologic appearance of the process is strikingly uniform and, as Pinner<sup>9</sup> remarks, "There is not only uniformity but monotony in regard to these lesions." The basic lesion is the epithelioid cell tubercle with occasional giant cells of the Langhans type and with an absence of caseation, and only occasionally some central necrosis. Because of the microscopic appearance, pathologists are prone to classify the disease as hyperplastic or non-caseous tuberculosis.<sup>10</sup>

Probably the most frequent sites of involvement, clinically, are the mediastinal lymph nodes and the pulmonary tissues, which makes the disease of particular interest to roentgenologists. We agree with Longcope<sup>6</sup> that it no longer can be regarded as a rarity. Since the lesions of sarcoid can occur in the lungs and mediastinum without cutaneous or other external manifestations, and since the pulmonary lesions, even though extensive, may exist without clinical signs, Roentgen examination of the chest plays an important rôle in its detection. Enlargement of the mediastinal lymph nodes is an almost invariable feature. The enlarged nodes produce soft, lobulated shadows in the hila or along the upper mediastinum, occasionally forming broad masses overlying the base of the heart and the great vessels. The outer borders are not as sharply delineated as is commonly seen in Hodgkin's disease and other forms of lymphoblastoma, but the extent of involvement may be almost as great. Such lymph node enlargement may occur with or without associated pulmonary lesions. When the lungs are involved, the lesions vary greatly in appearance. Usually widely distributed, they may appear as coarse, patchy densities; irregular striations; fibrous strands; or even as a uniformly disseminated, finely nodular or miliary process. The wide dissemination, the multiplicity of types of pulmonary shadows present and the concomitant mediastinal lymph

node enlargement are features which should lead one to suspect sarcoid.<sup>5</sup> When correlated with the clinical aspects and other laboratory data the diagnosis becomes more certain. The mildness of clinical symptoms often is entirely out of proportion to the extent of the disease as seen roentgenologically, and extensive lesions at times may be found more or less accidentally in the chest when there is little in the clinical picture to suggest their presence. Because of the usually benign nature of the process and the tendency for spontaneous recovery over periods of time, frequently a matter of several years, it may never be possible to obtain tissues for microscopic study and the diagnosis often must remain presumptive.

*Treatment.* Treatment has usually been purely empirical and includes the use of arsenicals, tuberculin, leprosol, iodides, gold salts, hyperpyrexia, ultra-violet irradiation, Roentgen rays and radium. The latter have been successful in the treatment of skin lesions, particularly the Darier-Roussy type, and also in the Boeck lesion.<sup>7</sup> Evaluation of any form of treatment is difficult because of the tendency of the lesions to spontaneous resolution.

Earlier workers have not found Roentgen ray therapy of benefit in the systemic lesions. Middleton<sup>8</sup> sums up this experience in the latest edition of Cecil's "Textbook of Medicine" with the statement that Roentgen ray and radium therapy offer nothing in this disease. Recently, however, several reports on the treatment of enlarged lymph nodes and of hilar and pulmonary sarcoid have been favorable. Harrell<sup>3</sup> treated 1 case, but at the time of the report the period of observation had been too short for evaluation; Bernstein and Oppenheimer<sup>1</sup> used Roentgen ray therapy in 4 of their 6 cases with very encouraging results; however, they believe that radiosensitivity may depend upon the stage of the disease at the time when treatment is instituted; and Katz *et al.*<sup>4</sup> report 1 case in which there was definite reduction in the size of hilar nodes following Roentgen irradiation. In the yearbooks of Radiology, no mention has been made of the use of Roentgen rays in the treatment of sarcoidosis, except for an editorial note suggesting a therapeutic trial because of the similarity of some of the cases to Hodgkin's disease.<sup>12</sup> British workers<sup>13</sup> report the treatment of hyperplastic tuberculosis by Roentgen therapy with good results, but the differential diagnosis is made between Boeck's sarcoid and hyperplastic tuberculosis. The terms are not used synonymously as they are in much of the American literature; consequently, it is impossible to determine whether or not some of the cases reviewed could be considered in the sarcoid group by the diagnostic criteria used in this country.

In order to obtain a more definite and current opinion regarding this problem, we sent questionnaires to 33 radiologists in this country and in Canada, chosen so as to give a fairly complete geographic representation. Four questions were asked: Have you treated patients with Boeck's sarcoid of the lung with Roentgen rays? If so, how many? What technique did you use? What were the results? Is there any other comment you care to make? Thirty-one replies were received

and the results are compiled in Table 1; the information given there speaks for itself. It seems apparent that very few cases of Boeck's sarcoid have been treated by Roentgen rays; the majority of those approached have had no experience with it and some advise against it.

In the past 2 years 14 patients have been treated by Roentgen rays for the chest lesions of Boeck's sarcoid in the Department of Radiology at the State of Wisconsin General Hospital; 8 of these have been observed sufficiently long to warrant certain preliminary conclusions. Within the period of observation, 6 of the 8 have shown definite roentgenologic evidence of improvement. In 2 cases the patients had been followed for periods of 22 and 23 months, respectively, before therapy was started, and the course in each case had been constantly progressive. It is of interest to note that clinical improvement preceded objective evidence in most cases, and that in the 6 cases in which roentgenograms demonstrated regression of the lesion, the objective improvement was manifested in from 2 to 4 months after therapy was started. Of the remaining 2 cases of the series, 1 showed improvement in 5 months after treatment, and the other patient failed to return for follow-up studies or treatment at regular intervals.

TABLE 1.—QUESTIONNAIRE ON ROENTGEN-RAY TREATMENT OF BOECK'S SARCOID

No.	No. of patients treated	Technique	Results	Comment
21	None			
1	..	....	....	Too few to express opinion
1	1	Not given	....	1 case with cervical nodes; favorable
1	1	Not given	Too early	Advise Roentgen ray therapy
1	1	75-150 r; 2× p.w., then 1/mo.	Very good	
1	2	2400-4800 r, 4 fields; HVLCu = 1 mm.	Recovery	Treats to differentiate between sarcoid and Hodgkins
1	3	100-200 r; 4-5 × 2 fields; HVLCu = 1.1 mm.	2 improved; 1 no follow-up	1 case also cervical nodes involved
1	3	100 r, 1 field daily; 500 r total per field; HVLCu = 1 mm.	1 improved, 2 not	Do not advise Roentgen ray therapy
1	4	HVLCu = 1.3 mm.; dose not given	Good	2 proved by biopsy; 2 had generalized involvement with visual disturbance; normal vision restored in 1
1	6	750-900 r divided in 3-4 doses A and P; HVLCu = 1 mm.	No benefit in most; 1 worse	Advise against Roentgen ray therapy
1	6	1200 r to each area; HVLCu = 1 mm.	No improvement	

The method of treatment has been 6 exposures of 150 r (in air) to the anterior and posterior mediastinum (15 x 20 cm. port), one area daily, using 175 kv., half-value layer = 1.05 mm. Cu. Patients returned in 6 weeks to 2 months and received a second series, using the same factors, except for 1 patient whose lesions had cleared almost completely in the interval. Two patients received a third series after a



second 2-month interval. Other glands involved usually receive 3 x 150 r (in air), daily or every other day, which may be repeated once or twice at intervals of 4 to 6 weeks.

**Case Reports.** CASE 1 (No. 11238). R. H., a 28 year old white male, was first seen at the State of Wisconsin General Hospital April 10, 1942, with the history of cough productive of  $\frac{1}{2}$  cup of mucopurulent, blood-flecked sputum for 6 months and of chest pain for a month. He complained also of dyspnea, wheezing, and hoarseness. His appetite was good, and he had had no weight loss. The symptoms were accompanied by a low grade fever up to 100° F. Physical examination was negative except for shotty cervical adenopathy and decreased resonance, increased vocal and tactile fremitus and decreased expansion of the right hemithorax. There were coarse rhonchi over the entire chest, but most pronounced at the right base. Laboratory findings were hemoglobin 14.8, R.B.C. 4,460,000, W.B.C. 6000 (neutrophils 65%, lymphocytes 31%, monocytes 2%, and eosinophils 2%); negative urinalysis; and a sedimentation rate of 27 mm. in 60 minutes. The tuberculin reaction was negative, and gastric aspirations for tubercle bacilli were negative by smear and by guinea pig inoculation. A roentgenogram of the chest showed soft thickening of the hilum shadows bilaterally, more pronounced on the right with associated soft infiltrative extension out into the mid- and basal lung fields (Fig. 1a). Roentgenograms of the bones of the hands were negative.

The diagnosis of Boeck's sarcoid was made and the patient was given Roentgen ray therapy to the mediastinum. When he returned for check-up examination after 3 months on July 17, 1942, he had resumed work; he had no dyspnea and very little cough; the chest roentgenogram showed marked improvement with clearing of the hilar thickening and of the soft opacity below the right hilum (Fig. 1b). He was last seen January 21, 1943, at which time he felt well and his chest had returned to normal.

CASE 2 (No. 11555). W. G., a 29 year old white male, was admitted July 20, 1942, with a history of non-tender swelling of the parotid glands bilaterally of 1 month's duration and associated with a low grade fever. He had had no dryness of the mouth nor noted other swollen glands. The systemic history was negative; he had had mumps as a child; there was no history of tuberculosis. Physical examination was negative except for firm, non-tender swelling of the parotid glands bilaterally; the liver was palpable just below the costal margin. Laboratory studies included a negative urinalysis; hemoglobin 16.6 gm., R.B.C. 5,370,000, W.B.C. 6950 (neutrophils 66%; lymphocytes 26%; monocytes 2%; and eosinophils 4%). A roentgenogram of the chest showed moderate, but definite enlargement of the hilum lymph nodes, more pronounced on the right side (Fig. 2a). A tentative diagnosis of Boeck's sarcoid was made.

The patient returned August 5, 1942 for biopsy and at that time the tuberculin test with 0.01 mg. and 0.1 mg. and the coccidioidin test were negative, as were gastric aspirations for tubercle bacilli. The total serum protein was 5.3 gm. with 3.5 gm. albumin, 1.8 gm. globulin and an A/G ratio of 1.9. A roentgenogram of the chest showed slight increase in hilum adenopathy. The biopsy of the parotid was diagnosed Boeck's sarcoid (Fig. 3a). Roentgen therapy was started to the mediastinum on August 8, and he received 6 treatments. He returned October 9 and was given a second series of 4 treatments. The parotid swelling had decreased, but there was no change in the roentgenogram of the chest. He received his third series starting January 18, 1943, at which time the roentgenograms showed almost complete regression of the hilum adenopathy. Following therapy, he developed some stringy density in the right upper lobe, but roentgenograms on November 29, 1943, showed regression of these lesions, and the patient continued to be symptom-free and afebrile (Fig. 2b).

CASE 3 (No. 11680). M. Jo., a 53 year old white woman, was first admitted to the State of Wisconsin General Hospital on July 13, 1942, with a severe menopausal syndrome and an associated vomiting and weight loss. Marked

hilar thickenings were noted on roentgenoscopic examination of the gastrointestinal tract, and subsequent roentgenograms of the chest showed marked

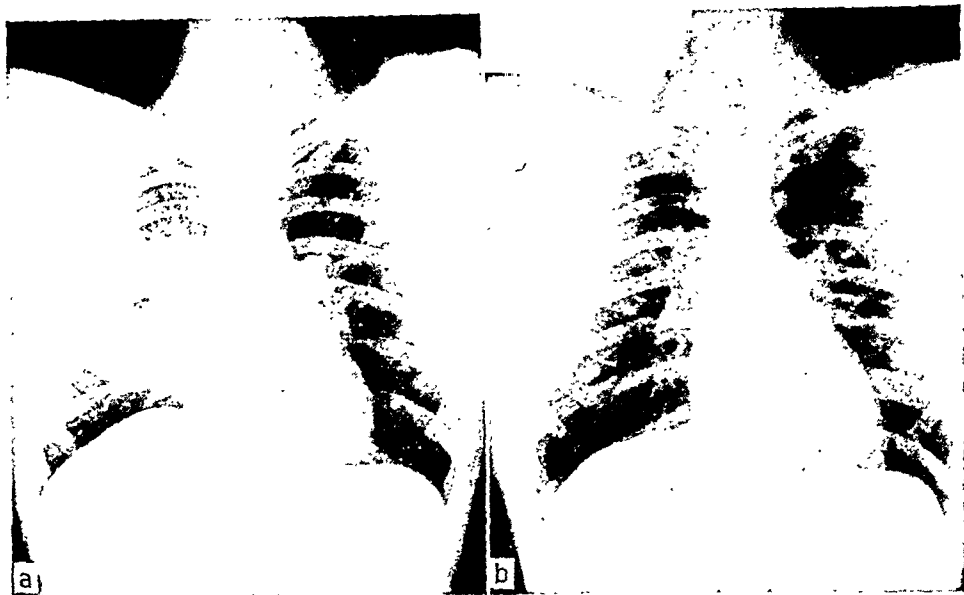


FIG. 1.—*a*, Soft thickening of the hilum shadows bilaterally, more pronounced on the right with soft infiltrative extension out into the mid- and basal lung fields (April 15, 1942). *b*, Clearing of the hilar thickening and of the soft opacity below the right hilum (July 17, 1942).

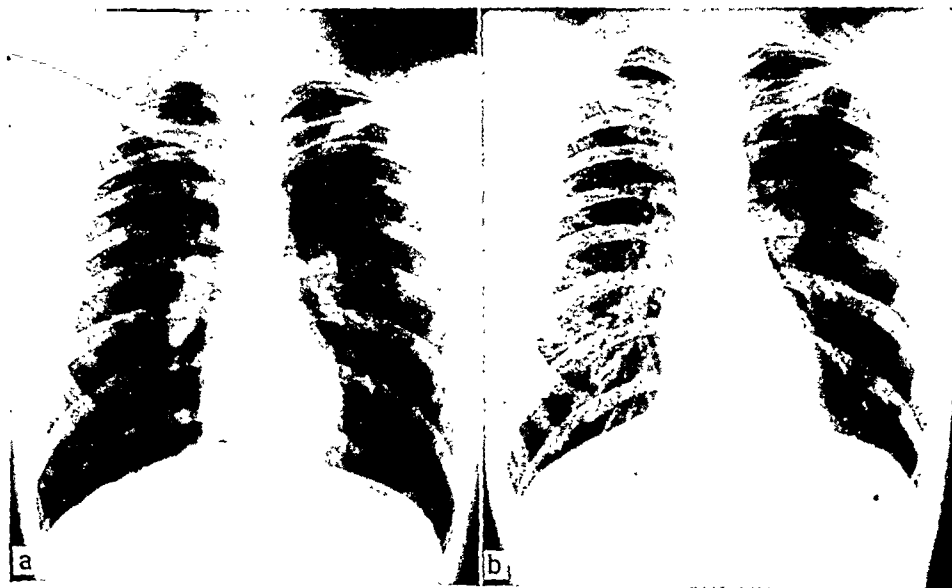


FIG. 2.—*a*, Moderate but definite enlargement of the hilum lymph nodes, more pronounced on the right side (July 22, 1942). *b*, Definite regression of lesions shown in *a* (November 29, 1943).

nodular thickening of both hilum shadows with associated coarse striated densities extending out into the mid-zone of the left lung field and toward the base on the right. She had no other adenopathy and neither chest findings

on physical examination nor symptoms referable to the chest. The urinalysis was negative; hemoglobin 13.3 gm., R.B.C. 4,300,000, W.B.C. 9000 (neutrophils 54%; lymphocytes 38%; monocytes 8%); gastric aspirations were negative for tubercle bacilli by smear and by culture; total serum proteins, 5.4 gm. with 2.1 gm. albumin, 3.3 gm. globulin and an A/G ratio of 0.6. The tuberculin test with 0.01 mg. and 0.1 mg., and coccidioidin tests were negative. A presumptive diagnosis of Boeck's sarcoid was made. The patient was discharged with medication for the control of the menopausal syndrome.

On September 20, 1942, she was readmitted because of intermittent sharp pain in the right lower chest and slight dyspnea and continued weight loss. Roentgen ray therapy to the mediastinum was started, but because the patient became nauseated only 5 treatments were given. A roentgenogram on December 2 showed definite regression of the hilar thickening. She was not seen again until March 3, 1943, when the chest showed almost complete clearing on the left with moderate enlargement on the right, and a second series of Roentgen ray treatments was given to the mediastinum. She was last seen on February 17, 1944, when she felt well, and the chest roentgenogram showed no residual on the left and only minimal thickening on the right.

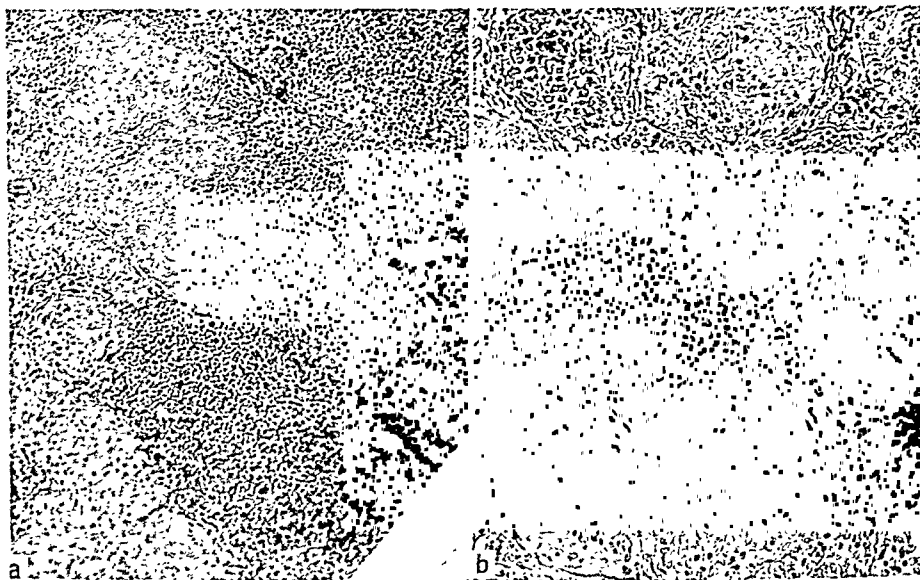


FIG. 3.—*a*, Photomicrogram of biopsy of the parotid gland in Case 2. *b*, Photomicrogram of biopsy of left axillary node of Case 6.

CASE 4 (No. 11761). I. Q., a 56 year old white woman, was admitted to the State of Wisconsin General Hospital with a history of nausea, loss of appetite, and weight loss of 20 pounds in the preceding 4 months. Systemic history was negative except for a dry cough. Physical examination revealed nothing of significance except a temperature of 101° F. The hemoglobin was 16.6 gm., R.B.C. 5,200,000, W.B.C. 4650 (neutrophils 59%; lymphocytes 39%; monocytes 2%); the urinalysis was negative. A roentgenogram of the chest showed distinct lobulated thickening of the hilum shadows on both sides and widening of the supracardiac shadow to the right and anteriorly due to involvement of the paratracheal lymph nodes. The pulmonary parenchyma was clear. A diagnosis of Boeck's sarcoid was made. She was readmitted on October 12, 1942; the roentgenogram of the chest showed no change and Roentgen therapy to the mediastinum was started. A second and third series were given in December, 1942, and in February, 1943. Roentgenograms showed slight, but definite regression on December 19, 1942, and return to normal on October 2, 1943.

CASE 5 (No. 12208). M. Ja., a 61 year old white female, was admitted to the State of Wisconsin General Hospital on March 23, 1943, with attacks of redness of the right eye with blurring of vision over a period of 3 years. In January, 1943, she had a more severe attack associated with pain; the family physician found the tension increased and started the administration of pilocarpine. The systemic history was not significant. Physical examination was negative except for the eyes. The urinalysis was negative; hemoglobin 16.9 gm., R.B.C. 5,260,000, W.B.C. 4350 (neutrophils 45%; lymphocytes 49%; monocytes 2%; eosinophils 4%); the total serum protein was 6.9 gm. with 3.4 gm. albumin, 3.5 gm. globulin and an A/G ratio of 0.97. A chest roentgenogram revealed scattered nodular infiltrations in the lung fields with an associated mild tracheobronchial lymphadenopathy. A diagnosis of sarcoidosis with chest involvement, uveitis and secondary glaucoma was made; local treatment was administered to control the glaucoma and Roentgen ray therapy to the mediastinum was started. The patient returned May 26, 1943, for follow-up examination. The glaucoma had been well controlled, but the chest lesions had advanced moderately. A second series of Roentgen ray therapy was given to the mediastinum. The patient failed to return until January 26, 1944. She had discontinued the use of the prescribed eye drops and reentered the hospital because of a recurrence of symptoms of glaucoma. A roentgenogram of the chest showed minimal regression of the nodular lesions. The tuberculin tests, both 0.01 mg. and 0.1 mg. were negative. The patient refused to remain for further Roentgen ray therapy.



FIG. 4.—a, Numerous coarse nodular shadows in the parenchyma, more numerous in the upper two-thirds and associated with fibrous strands extending out from the soft, well-defined, enlarged hilar nodes bilaterally (June 6, 1941). b, Definite regression of lesions shown in a (March 16, 1944).

CASE 6 (No. 10444). H. D., a 34 year old white male, was first admitted to the State of Wisconsin General Hospital on June 15, 1941, with the history of swelling of the cervical, axillary and inguinal glands since 1938, and of increasing dyspnea and dysphagia. In February, 1941 he had had a tonsillectomy, because of frequent colds and sore throats; healing was delayed. At that time, a node from the left axilla had been biopsied and was reported hyperplastic tuberculosis (Fig. 3b). The patient was sent to a sanatorium where he was always afebrile and repeated tuberculin tests and gastric aspirations for tubercle bacilli were negative. On physical examination at the time

of admission, a small ulcerated lesion was noted in the left nostril; this had been present for 2 or 3 years. There was also a generalized adenopathy, and a palpable liver and spleen. The chest was negative. The hemoglobin was 15.2 gm., R.B.C. were 5,370,000, W.B.C. 7350 (neutrophils 79%; lymphocytes 11%; monocytes 8%; eosinophils 2%); gastric aspirations for acid-fast organisms and tuberculin tests remained negative and the sedimentation rate was 21 mm. in 60 minutes. The roentgenogram of the chest showed numerous coarse, nodular shadows in the parenchyma, more numerous in the upper two-thirds and associated with fibrous strands extending out from soft, well-defined enlarged hilum nodes bilaterally (Fig. 4a). At that time, Roentgen ray therapy was given to the cervical nodes, 3 x 150 r (in air), 175 kv., half value layer = 1.05 mm. Cu, 10 x 10 cm.<sup>2</sup> field, and he was returned to the sanatorium.

The patient was seen at intervals for the next 2 years and received further therapy to various enlarged glands with good results. Although the chest lesions progressed as shown in the roentgenograms, gastric tests remained negative and the patient was discharged from the sanatorium.

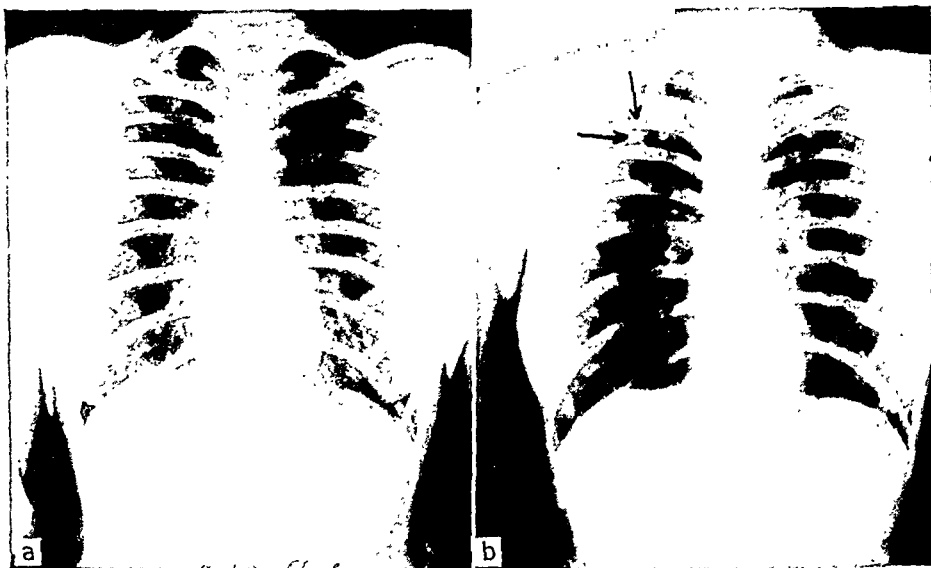


FIG. 5.—a, Normal chest (November 11, 1940). b, Moderate nodular thickening of the hilum shadows bilaterally; general soft accentuation of trunk markings in both lungs with a small area of nodular infiltration in the right apex (see arrows) (June 23, 1941).

On March 2, 1943 he was again admitted to the State of Wisconsin General Hospital for further studies. He had minimal shotty adenopathy, the previously mentioned lesion in the left nostril, and in addition a 3 cm. red, non-tender nodule in the right axilla and bilateral dacrocystitis. The blood count and urinalysis were normal; the total serum protein was 7.5 gm. with 3.2 gm. albumin, 4.3 gm. globulin, and an A/G ratio of 0.7; coccidioidin skin tests were negative. Roentgenograms of the bones of the hands and feet showed no cystic lesions. Roentgen ray therapy to the mediastinum was then given. On June 22, 1943 a roentgenogram of the chest showed some increase in the lesions, but the patient was unable to remain for treatment. However, when he returned for the second series August 23, early signs of resolution were apparent, and he was working for the first time in more than 2 years. When last seen on March 16, 1944, the chest lesions had undergone uniform regression in size, and there was no significant adenopathy (Fig. 4b).

CASE 7 (No. 12342). E. D., a 22 year old white woman, was first seen for routine examination at the time of employment by the State of Wisconsin

General Hospital on August 31, 1939, when physical examination and chest roentgenogram were essentially negative. A routine chest roentgenogram on November 11, 1940 (Fig. 5a) was also negative. On June 23, 1941 she asked for an examination because of substernal pain of 1 week's duration and throat clearing for the preceding 2 or 3 months. Her weight had been at the lower limits of her normal variation for several months. Chest roentgenograms demonstrated distinct, but moderate nodular thickening of the hilum shadows bilaterally and rather general soft accentuation of trunk markings in both lungs, together with a small area of nodular infiltration in the right apex (Fig. 5b). W.B.C. numbered 6050 (neutrophils 50%; lymphocytes 47%; monocytes 2%; eosinophils 1%); gastric aspirations for acid-fast organisms by smear and by guinea pig inoculation were negative.

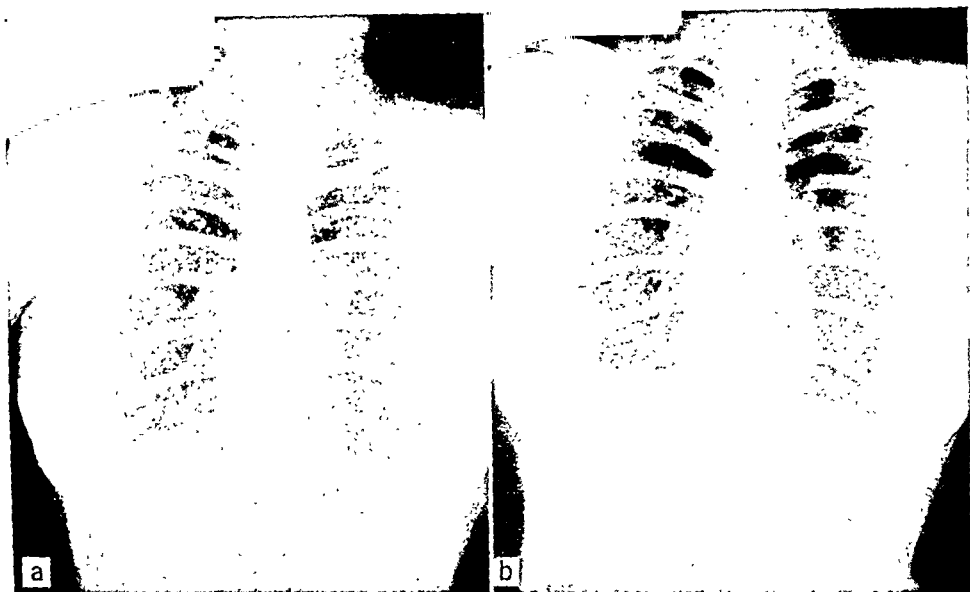


FIG. 6.—a, Further increase in the pulmonary lesions shown in Figure 5b (November 19, 1942). b, Bilateral hilar thickening and fine granular nodularity with some stringy density throughout the lung fields (June 2, 1943).

During the following 2 years the patient was kept at strictly limited activity and followed closely. She was afebrile, had no cough or expectoration, had gained weight, but the substernal pain persisted and she developed mild arthralgia of her hands and feet. Repeated gastric aspirations remained negative for tubercle bacilli except on one occasion when one organism was found in the smear, but the culture from the same specimen was negative. The tuberculin test with 0.01 mg. was negative; 0.1 mg. gave a  $2 \times 2$  cm.<sup>2</sup> reaction. About 1 year after the onset, her menses became irregular and a mass 4 to 5 cm. in diameter was found on the right side of the pelvis. There was a gradual increase in the pulmonary lesions (Fig. 6a) until a chest roentgenogram in June, 1943 showed bilateral hilar thickening and fine granular nodularity with some stringy density throughout the lung fields (Fig. 6b), and a presumptive diagnosis of sarcoidosis was made. Roentgen ray therapy to the mediastinum was started June 3, 1943. On August 2, 1943 a roentgenogram of the chest showed slight, but definite regression of the lesions, and a second series of treatments was given. The roentgenogram taken on October 4, 1943 (Fig. 7a) demonstrated almost complete clearing of the process, and in follow-up studies on March 6, 1944 and June 5, 1944 (Fig. 7b) there was no evidence of recurrence.

CASE 8 (No. 12712). D. F., a 48-year old Jewish woman was admitted to the State of Wisconsin General Hospital on October 19, 1943 with the history

of hard, painful nodules on her legs for the preceding 9 months; vague joint pains particularly in her wrists and fingers for 6 or 7 months; episodes of cramping abdominal pain and fever for 3 months; and a feeling of oppression in her chest of 3 to 4 months' duration. On physical examination the nodules were observed to be discrete, firm, immovable, red or bluish red, and varying in size from 1 to 4 cm. There was no adenopathy; the liver was palpable 3 cm. below the costal margin; the spleen was not palpable. There were a few moist râles at both lung bases and there was a soft systolic murmur at the cardiac apex transmitted to the left axilla. The urinalysis was negative; the hemoglobin was 14.3 gm., R.B.C. were 5,000,000, W.B.C. 6800 (neutrophils 71%; lymphocytes 20%; monocytes 4%; eosinophils 5%); sedimentation rate 4 mm.

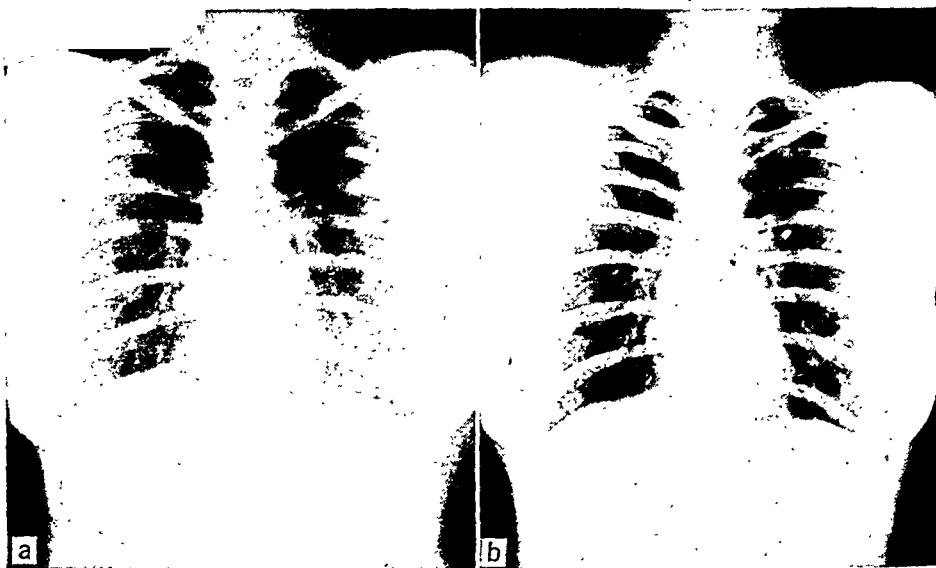


FIG. 7.—*a*, Almost complete clearing of the process shown in Figure 6*b* (October 4, 1943). *b*, No evidence of recurrence approximately 1 year after the treatment (June 5, 1944).

in 60 minutes; the ECG was normal. Roentgenographic findings were lobular thickening of the hilum shadows on both sides of fairly soft character with mild accentuation of trunk shadows in the lower lobes bilaterally. A diagnosis of erythema nodosum and Boeck's sarcoid was made and Roentgen ray therapy to the mediastinum given. The patient returned December 27, 1943 for a second series of treatments. The chest remained unchanged, but the patient had improved clinically. Likewise no change was demonstrated when the patient was seen in February, 1944, but on the examination May 24, 1944, definite regression was found.

**Comment.** The relatively small number of cases does not permit a statistical evaluation of the age and sex distribution beyond the statement that the majority of the patients were females and belonged to the middle-aged group. No definite relationship between type and severity of involvement, duration of the disease and response to treatment can so far be established. In 2 instances the diagnosis was proved by biopsy; in the remaining patients it rested on Roentgen examination only. In 4 of the first 8 cases the therapeutic result was good, in 1 instance excellent, in 1 satisfactory and in 2 only fair. The

patient described in Case 7 is perhaps the most interesting and convincing one because of the long duration and progressive character of the pathologic process as proved roentgenologically—2 years before Roentgen ray therapy—and because of the striking response to treatment. No untoward reactions were observed in any one of the treated cases, and therefore we would like to encourage other radiologists to give Roentgen ray therapy in Boeck's sarcoid a trial. More observations and further studies are, of course, necessary before a final verdict as to the efficacy of the treatment proposed can definitely be determined.

**Summary.** 1. The pathologic aspect and the Roentgen diagnosis of Boeck's sarcoid are briefly discussed.

2. Our experience with Roentgen rays in the treatment of this disease, based on the study of 14 patients, 8 of which were observed sufficiently long to draw preliminary conclusions, is related.

3. Since the results were favorable in the majority of cases and no untoward effects observed, the use of Roentgen rays in the treatment of Boeck's sarcoid is recommended in order to arrive at a definite opinion regarding its true efficacy.

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## THE TREATMENT OF TULAREMIA WITH INTRAVENOUS BISMUTH SODIUM TARTRATE

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TULAREMIA is showing an increasing incidence. It is possible that it is being recognized more frequently. It would seem constructive and timely, therefore, to present a new and effective form of treatment. With the exception of a few general comments concerning



incidence, morbidity and mortality, this report will be limited to its diagnosis and clinical management.

In reviewing the literature it becomes apparent that considerable confusion exists regarding the methods of transmission of tularemia and its various types, their morbidity and mortality.

*Pasteurella tularensis* (*Bacterium tularense*). In 1912, it had been found in more than 20 forms of wild life (McCoy and Chapin) and since then many others have been added. The current list includes rabbits, hares, squirrels, prairie dogs and a variety of small fur-bearing animals, both wild and domestic—sheep, dogs, cats, rats and mice; numerous fowls—quails, sage hens and chickens; and various arthropods such as flies, fleas, bed-bugs, ticks and lice.

The last-named group is usually responsible for animal-to-animal transmission, while man may become inoculated by handling the fur or tissues of the infected animal, by eating its meat, by inhalation of dust containing the organism, by handling the pasteurella in the bacteriologic laboratory, or by a direct bite of one of these insects, particularly the ticks (wood tick—*Dermacentor andersoni*, and dog tick—*Dermacentor variabilis*). Here in Arkansas at least 90% of our cases result from tick bites, and it is disturbing to note that in ticks, hereditary transmission has been demonstrated through eggs, larvæ and nymphs.<sup>1</sup>

Tularemia is a relatively recent disease. The causative organism was first isolated from ground squirrels in 1911 by McCoy and Chapin<sup>2</sup> in Tulare County, California, while first clinical recognition was by Wherry and Lamb in 1914.<sup>3</sup> Cecil<sup>4</sup> now records over 10,118 known cases in 46 states and the District of Columbia. He further points out that although tularemia occurs in every month of the year, it is most prevalent in tick regions in March to August, deerfly areas June to September, due to jack rabbits in April to October, and cottontail rabbits in November and June. Foreign distribution includes Canada, Scandinavia, northern and eastern Europe, Russia, Turkey and Japan.

The usually described forms of tularemia are those most frequently encountered. They include (1) the ulceroglandular type, which exhibits an ulcerating papular lesion at the site of inoculation, with definite regional lymphadenitis, with or without suppuration; (2) the glandular type, presenting the lymphadenitis without the primary lesion; (3) the oculoglandular type, with initial infection of the conjunctiva and secondary participation of neighboring lymphatics; (4) the oral, or anginal form, usually acquired by eating inadequately cooked infected meats, and characterized by an acute, painful, ulcerative pharyngitis or nasopharyngitis, enlargement of the submaxillary and cervical lymph nodes, and gastro-intestinal manifestations; and (5) the "typhoid," or cryptogenic type, which presents a toxemia with a prolonged and debilitating pyrexia, but without the primary lesion or lymphadenitis. This latter type is seen most frequently in laboratory workers.

Pleuropulmonary manifestations<sup>5</sup> are often recorded, including atypical pneumonia, lung abscess, acute or chronic bronchitis and

pleurisy with effusion, accompanied by mediastinal and peribronchial lymphadenitis. Meningeal or leptomeningeal involvement, usually fatal, has been reported with recovery of *B. tularensis* from the spinal fluid, and diffuse encephalitis in acute tularemia has been demonstrated at autopsy by Hartman. Foshay<sup>6,7</sup> has discussed coronary occlusions and angina pectoris as tularemic complications, Saphir<sup>8</sup> has dealt with myocarditis, while Aagaard<sup>9</sup> recently reviewed the pericardial involvements, reporting 2 adult cases.

In some quarters tularemia appears to be regarded as a trivial affair, tending to spontaneous recovery with a minor degree of morbidity and a mortality rate of less than 5%. This would seem to apply only to a select group of the mild uncomplicated infections. Cecil<sup>4</sup> quotes Foshay, "The mean duration of fever is 26 days, the duration of the adenopathy from 3 to 4 months, and the duration of the disease 5½ months." He points out that pulmonary tularemia has a "high rate of fatality (62.5%)." Averaging all types, Foshay cites a mortality of 6%; Simpson 11%; Jager and Ransmeier<sup>10</sup> review 9 cases of constrictive pericarditis with 33% mortality, while Stitt, Clough and Clough<sup>1</sup> mention 12 fatalities of 20 cases resulting from the ingestion of insufficiently cooked rabbit meat.

From the Shreveport Louisiana Charity Hospital, W. R. Mathews<sup>11</sup> reports similarly acquired infections with 4 deaths in a family of 5, exhibiting acute pharyngeal lesions suggestive of diphtheria. He states the tularemic mortality in that hospital to be "approximately 11% for white patients and 32% for colored."<sup>12</sup>

In this region tularemia is frequently encountered. In the past 3 years I have seen or been consulted about 61 cases. All have been treated by the intravenous injection of a water-soluble bismuth, with prompt recovery, while within the limited investigations we have been able to conduct, we have learned of no case of tularemia with positive blood cultures, other than the ones treated with intravenous bismuth, which have lived for more than 14 days.

The geographic distribution of these 61 cases was Arkansas, Oklahoma, Missouri, Kansas, Louisiana and Texas. All but 3 were within the area bounded by the water sheds of the Red River on the south and the White River on the north.

In 57 cases the source of infection was a tick bite; 1 was a squirrel bite; 3 were hand infections, acquired by skinning rabbits. Since the tick plays the dominant rôle as the source of infection in this region, most of the patients have been loggers or farmers working in wooded tracts with brush undergrowth.

Six cases were Negroes, 55 were whites. All Negro cases were of the mild "typhoid" type, none presenting acute throat symptoms. This limited number did not permit confirmation of the observation by Mathews that in the Red River section the Negro death rate is 3 times that of the white man.

Every tularemic tick bite on the lower extremity developed a bubo on the corresponding side. In no case was this bilateral. Two cases presented lesions on the penis, one an ulcer on the dorsal corona, the other an ulcer on the anterior surface at the base of the shaft. One of these developed a right-sided bubo, the other a left.

Twenty-one cases with lesions on the arms or upper torso all showed an axillary adenitis, but in only 2 did the glands progress to suppuration. No reason is apparent as to why the inguinal glands break down and the axillary do not. Epitrochlear glands suppurred in 2 cases, the same forearm in each case presenting the initial lesion.

In this series, the incubation period has been within relatively fixed limits. The initial chill and malaise occurred between 72 and 120 hours after discovery of the tick and its removal from the skin.

Agglutination tests were routinely done on all cases when first seen. All but 2 showed positive titers of 1:360 or over. Of these 2 the titers reached 1:360 in 1 on the 17th day and in the other on the 18th day. The treatment employed did not interfere with the agglutination titer.

Blood cultures were made on 50 cases of the lymphoglandular type, with only 16 proven positive. The mild typhoid type cases were not cultured.

The inoculation of laboratory animals with the patient's blood, or material obtained from the glands or other lesions, was not employed, due to the inherent delay of the procedure in serving as an aid in diagnosis.

**Treatment.** We are familiar with the purely symptomatic treatment of these cases and have tried the various therapeutic agents suggested from time to time, without impressive results. Our experience with the Foshay Specific Antiserum has been disappointing, and more recently a trial of several of the sulfonamide compounds resulted in no clinical improvement whatever. Two of my associates, who have had an opportunity to conduct significant trials of penicillin in combating this gram-negative bacillus, report it to be ineffective. With none of these methods has symptomatic relief been striking or the return to usual activities as prompt as with the use of intravenous bismuth.

**Bismuth Treatment.** Intravenous injections of the bismuth solution were started in all of these cases at the time of their first visit, without awaiting laboratory findings. In most instances this was on the 3rd or 4th day after the patient was aware of being sick. Early diagnosis and treatment is imperative with other than the mild typhoid type of tularemia. If treatment is postponed, particularly in those cases presenting positive blood cultures, the death rate will be extremely high. Even in persons gravely ill, because of the delay in completing titrations, and in view of the high percentage of negative cultures from initial lesions, glands or blood in the early stages of the infection, the diagnosis must be made and treatment started without the aid of the laboratory. Usually the characteristic clinical onset and the history of exposure to probable infection will supply the necessary evidence.

Originally we employed other aqueous bismuth preparations, but during the last 2 years we have used a solution of bismuth sodium tartrate, prepared especially for experimental intravenous use.\* It

\* Supplied by G. D. Searle & Co. A 2% bismuth sodium tartrate solution containing 29.6 mg. of bismuth per cc., and buffered with sucrose to isotonicity.

appears more effective than any of the bismuth salts previously employed, possibly due to the chemical nature of the bismuth complex.

The solution does not irritate the vein intima, and in our experience any local inflammation has been due to the inadvertent injection of it outside the vein. We routinely employ a 25 to 26 gauge needle to avoid injury to the vein walls.

Untoward effects have been practically *nil*. Reactions of nausea and vomiting are seen occasionally, but much less frequently than with any of the arsenicals. In the few persons who developed nausea immediately after the injection, a level teaspoonful of sodium bicarbonate in water, orally, minimizes this gastric symptom. In no case has it been necessary to stop the injections.

No circulatory evidence of shock has ever been seen. Although diarrhea has occurred rarely in the course of treatment of other conditions by intravenous bismuth, it has been encountered in none of these tularemias.

Gingivitis has not occurred in any case in this series. It is far less common than with the intramuscular use of bismuth, and only 2 cases of gingivitis have been observed in 7 years' experience with intravenous bismuth administration.

The dose is estimated on the basis of 1 cc. to 100 pounds of body weight. In children under the age of 15 the dose may be relatively larger, estimated at approximately 1 cc. for 40 to 50 pounds of weight. For an adult the initial injection is 1 to 1.25 cc. to test the tolerance of the patient. Through a small needle the speed of injection is of no importance. If nausea does not follow the first injection, the dose is increased according to the weight scale, at the next injection. This dose is administered intravenously each day until the temperature reaches a daily maximum of 99°. The injections are then given on alternate days for 4 treatments, then twice a week for 4 more weeks.

In our scheme of treatment the necrotic glands are not incised. Instead, the skin is infiltrated with novocain, a sharp No. 18 needle is plunged into the gland and the contents aspirated with a Luer syringe. By this release of pressure from the overlying skin, necrosis is prevented and suppuration with drainage avoided.

The average number of bismuth injections required to secure the clinical picture of recovery has been 7; the smallest number was 4; the longest series of daily injections necessary to establish a normal temperature, with clinical evidence of recovery, was 18.

In this series of 61 cases of tularemia treated with intravenous bismuth sodium tartrate, no death has occurred. It has proved, in this area, a specific procedure in the treatment of this disease.

*Bismuth Intravenously.* In view of the widely prevalent belief that bismuth should never be administered intravenously, a comment or two on this misconception may be in order.

In the past 7 years 90,000 intravenous injections of bismuth have been given to nearly 700 patients. The diseases have included lues, bronchial spirillum infections, bronchiectasis, pulmonary tuberculosis, acute tonsillitis, actinomycosis and tularemia. In no instance

has there been a reaction to compare in severity with that which frequently accompanies the intravenous use of the arsenicals.

Children tolerate intravenous bismuth especially well. Numerous youngsters from 4 to 7 years have received from 0.75 to 1 cc. of the currently employed solution, twice weekly for 6 months or more without untoward effects of any type. In these ages the tolerance of a 40 pound child appears to be approximately 1 cc. These prolonged series of injections were in the treatment of pathologies other than tularemia, and are mentioned here only in refutation of the commonly accepted dictum that intravenous bismuth is highly toxic to the human. The statement has been made by numerous pediatricians that *children* do not stand bismuth well, referring to its intramuscular injection. By intravenous administration we have not found this true.

There is the hypothesis that intravenous bismuth might prove effective against some of the rickettsias; we have typhus particularly in mind. Typhus does not appear in this section in sufficient numbers to provide an opinion, but it is hoped that bismuth sodium tartrate will be tried intravenously by clinicians having such cases available.

The toxicity of the older monotartrate of bismuth is not characteristic of the more recent aqueous soluble forms, when employed intravenously in the human. As compared with the intramuscular administration the intravenous routing provides definite differences in clinical action, all advantageous. The dictum that bismuth is a one-way drug, *i. e.*, intramuscular, is nonetheless false because it has been, and is being today, solemnly intoned.

Sufficient for the clinician is the knowledge that a drug is safe and non-toxic within reasonable limits, and that it carries the potential of benefit or cure for a disease entity. Bismuth sodium tartrate intravenously, so serves against tularemia.

**Case Reports.** CASE 1. B. J., male Negro, age 7, weight 42 pounds. His dog caught a rabbit Sept. 5, 1943, and he and his 2 companions skinned it. It was not eaten by any members of the family, contrary to usual rule.

The ulcer developed at the base of the nail, second digit, right hand, where previously he had had a scratch. His chill, temperature and malaise developed 94 hours after skinning the rabbit. Neither of the other 2 boys became ill.

He was first seen 6 days after the contact. His temperature was 102°, a lymphadenitis was present in both epitrochlear and axillary regions, most marked on right. The blood titer was 3+ in 1:360 dilution.

Intravenous injections of bismuth sodium tartrate, 1 cc. daily, were started on the day first seen. Since children under 12 years of age tolerate intravenous bismuth in twice the weight-scale of adults, this boy with a weight of 42 pounds, showed no evidence of excessive dosage.

The axillary glands did not break down, conforming to our routine experience. He received 4 daily intravenous injections, all during office visits. He was not restricted to bed at any time. The temperature remained below 99° after the fourth injection. He then received 8 more injections, 2 per week, with complete recovery.

CASE 2. R. L. W., male, white, age 17, weight 125 pounds. Always a resident of New York City, he came to visit a farm near Hot Springs, Ark., May 2, 1943. While roaming about the woods the first day, he received multiple tick bites on both legs and thighs. One small ulcer developed on the right anterior tibial region, the site from which a tick had been removed 84 hours prior to the initial chill and malaise.

Bismuth sodium tartrate was given intravenously when first seen, after taking a blood specimen for agglutination tests. The titer was 4+ in 1:360 dilution on the first test. The bismuth solution dosage was 1 cc. to 100 pounds of weight.

He received 5 daily injections, followed by 2 per week for 3 weeks. The temperature remained below 99° after the fifth daily injection. All injections were given at the office.

A bubo developed in the right inguinal chain, conforming to the observation that in these cases the inguinal glands will break down on one side only, while the axillaries will enlarge but not suppurate.

This patient lost no weight, was not confined to bed at any time, and returned to New York within a month of his infection, fully recovered.

CASE 3. J. W. L., male, white, age 55, weight 175 pounds.

On the evening of May 22, 1943, after a day of cutting brush on his farm, two ticks were removed from the right upper arm at the insertion of the deltoid muscle. The initial chill, followed by temperature and malaise, occurred 80 hours after the ticks were discovered.

The attending doctors suspected tularemia but remained uncertain for 18 days, during which time they submitted daily blood specimens to the laboratory in an effort to obtain a positive agglutination titer. The titer on the 18th day was a 4+ in a 1:360 dilution. During this 18-day period he had received sulfathiazole and aspirin, with no effect upon his temperature, which had a daily range to 104° and 105°. He had lost 32 pounds of weight.

Intravenous bismuth sodium tartrate was started the 18th day, and given daily in a dosage based on 1 cc. to 100 pounds of weight.

At the time of the seventh daily injection the temperature remained below 99.6° the entire day. Injections were then given on alternate days for 12 days, during which the temperature remained below this level. He then received 2 injections per week for 6 weeks. He was able to come to the office for treatments 15 days after the first injection, and thereafter progressed to uneventful recovery.

This case illustrates the hazard of awaiting laboratory confirmation of tularemia, since the positive titer may be delayed, and such delays in treatment make serious inroads on the resistance of the patient. Tularemia can always be diagnosed clinically; the laboratory findings are only confirmatory.

**Conclusion.** Sixty-one consecutive cases of tularemia are reported, including various types, all treated, with prompt recovery, by intravenous injections of a solution of bismuth sodium tartrate, especially prepared for intravenous application.

The use of this solution has proved a specific procedure in the treatment of tularemia.

Contrary to prevalent views, the intravenously administered bismuth is quite free from serious untoward manifestations. This opinion is based upon some 90,000 intravenous injections in approximately 700 cases, extending over a period of 7 years, and including a variety of pathologic conditions.

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## VITAMIN CONTENT OF LIVER EXTRACTS FOR PARENTERAL USE

### A COMPARISON OF CRUDE AND CONCENTRATED PREPARATIONS

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IN this brief paper we shall attempt to answer the frequent requests for quantitative data on the vitamin B factors present in liver extract for parenteral use. The quantitative variations in the several factors present in different brands of liver extract are in part due to the distinct processes employed. Since we are dealing with preformed substances stored in liver, the amount of which is dependent in part upon the nutrition of the animal, it is obvious that even when employing the same extraction process there may be some variations in yields. It is hoped that a comparison of the data on the concentrated extracts with those on the crude extracts will be of help in evaluating these dilute, unrefined preparations.

**Material and Methods.** The liver extracts, conforming to U.S.P. standards, included in this report represent random samples of leading brands obtained through a wholesale druggist and, through our Control Laboratory, unselected samples of our own manufacture. These extracts have been assayed by the microbiologic methods now in general use for riboflavin,<sup>3</sup> niacin,<sup>4</sup> pantothenic acid<sup>5</sup> and *L. casei* factor (Bc)<sup>2</sup>. Total solids and total nitrogen values are also included. For various reasons it has not been possible to determine pyridoxine (B<sub>6</sub>) or choline. Since the thiamine content of parenteral liver is negligible, this factor is omitted from the study. The data presented in Table 1 reflect in a relative manner the effects of the various processing procedures.

In recent years numerous references to the use of "crude" liver extract have appeared in the medical literature. The confusion caused by the loose use of this term should come to an end now that the First Supplement of U.S.P. XII (p. 36) contains a definition of "Liver Injection (Crude)." Although each manufacturer of liver extract prepares material corresponding to Cohn's G fraction, there are many modifications of the original procedure which, in turn, result in marked differences in color, in the content of total solids, total nitrogen, the anti-anemic substance and the several components of the B complex. One of the steps in general use calls for the addition to a syrupy concentrate of the original water extract of sufficient 95% alcohol to obtain

a mixture containing 65% alcohol by volume. The anti-anemic substance, plus varying amounts of the B complex factors stay in solution in the water-alcohol mixture, leaving a voluminous tarlike residue which contains by far the major portion of the B complex factors (extracted by water in the first stage). This step is essential, as it is the principal means by which proteins and other inert substances are removed from the original extract; and so it makes possible the preparation of injectable solutions. The processing steps from this point on are quite different and each manufacturer is careful to protect his methods of purification and concentration. Apparently those who favor the parenteral use of the crude liver extracts are not employing such material in the treatment of pernicious anemia, but use the crude preparations for non-specific therapy principally because of the belief that larger amounts of the several B complex factors are present in these crude extracts.

**Results.** The results of the analytical work (calculated per cc. and per U.S.P. XII unit injectable) are presented in Table 1. As the standard for comparison in our study of liver extracts we have prepared the crude, unfractionated extract obtained as the first step in the manufacture of all liver preparations, No. 21e in Table 1. It is important to an understanding of this discussion to keep in mind that this crude extract contains the maximum amount of each of the several B factors extractable from whole liver by an acid-water infusion, pH 5±. Using this material as a "yard stick" and taking extract No. 1 in Table 1 as an example, we have in this refined and concentrated extract only 1.5 µg. of riboflavin as compared with 1914 µg. in the crude standard. In other words, only 0.08% of the riboflavin content of the crude extract remains in the highly concentrated material. Using the same unfractionated extract as the standard, an examination of the data for each of the 6 highly refined and concentrated preparations (containing 15 units injectable per cc.), Nos. 1 to 6 in Table 1, shows that the content of:

Riboflavin	varies from 0.08 to 10.7%	of quantity present in the standard				
Niacin	" " 1.4	" 40.0%	"	"	"	"
Pantothenic acid	" " 0.6	" 32.0%	"	"	"	"
<i>L. casei</i> factor (B <sub>c</sub> )	" " 0.08	" 1.0%	"	"	"	"

Similarly, a study of the data for each of the 3 crude extracts, Nos. 11, 12, 13c, Table 1 (2 units injectable per cc.), shows that the content of:

Riboflavin	varies from 0.07 to 4.8%	of quantity present in the standard				
Niacin	" " 4.00	" 16.0%	"	"	"	"
Pantothenic acid	" " 3.60	" 18.0%	"	"	"	"
<i>L. casei</i> factor (B <sub>c</sub> )	" " 0.09	" 7.0%	"	"	"	"

Those who favor the parenteral use of the crude liver extracts are not primarily interested in the treatment of pernicious anemia; hence there would appear to be no reason to make comparisons based on the values obtained when the several B factors are shown in relation to



TABLE 1.—ANALYTICAL DATA ON LIVER EXTRACTS

Sample	U.S.P. units per cc.	Total solids Milligrams		Total nitrogen Milligrams		Riboflavin Micrograms*		Niacin Micrograms*		Pantothenic acid Micrograms*		L. casei factor (B. o) Micrograms*			
		Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit	Per cc.	Per unit		
1	15	73	5	8	0.5	<i>Parenteral Liver Extracts</i>						1210	81	0.73	0.05
2	15	216	14	22	1.4	1.5	0.1	2290	153	1210	81	5.56	0.37		
3	15	194	13	28	1.9	99.6	6.6	205	14	185	12	8.72	0.58		
4	15	235	10	33	2.2	205.0	13.7	109	7	31	2	2.66	0.18		
5a	15	79	5	13	0.9	136.5	9.1	1270	85	155	10	0.88	0.06		
6b	15	215	14	27	1.8	2.1	0.1	204	14	5	0.4	0.75	0.05		
7	10	103	10	13	1.3	1.9	0.1	3160	211	1710	114	0.40	0.04		
8	10	99	10	10	1.0	1.0	0.1	1316	132	816	82	0.20	0.02		
9	4	329	82	23	6.8	9.3	0.9	1600	160	940	94	2.22	0.55		
10	3.3	178	54	14	4.3	51.6	12.9	1430	358	379	95	2.63	0.80		
11	2	295	148	35	17.5	1.2	0.4	270	81	191	58	4.06	2.03		
12	2	290	145	20	10.0	92.7	46.4	305	153	191	95	0.76	0.38		
13c	2	349	175	31	15.3	76.0	38.0	1220	610	330	165	1.01	0.50		
14	1	256	256	16	16.0	2.2	1.1	954	477	569	285	3.67	3.67		
15	1	143	143	9	9.0	26.4	26.4	672	672	272	272	0.20	0.20		
16d	1	177	177	16	16.0	31.3	31.3	614	614	98	98	1.09	1.09		
17	60 cc.-I.U.	143	8,580	9	540.0	<i>Oral Liver Extracts</i>						150	9,012	0.21	12.30
18	.45 cc.-I.U.	121	5,445	9	423.0	0.5	31.7	349	20,940	150	9,012	2.60	117.00		
19	45 cc.-I.U.	517	23,260	38	1724.0	34.1	1,534.5	327	14,670	88	3,960	1.69	76.00		
20	12.75 gm.-I.U.	..	..	91k	1160.0k	232.0	10,422.0	1010	45,450	235	10,575	5.92k	75.50k		
21e	Unfractionated Conc.	..	..	59m	..	254.0k	3,237.2k	792k	10,096k	449k	5,725k	57.60m	..		

\* 1 mg. = 1000  $\mu$ c. (or gammas).

a Not a domestic product but appears in the list of U.S.P. products.

b Made by an approved process; standardization in progress.

c Made by an approved process; standardization in progress.

d A dilution of c with equal volume of normal saline solution.

e A concentrate of the total extractives obtained by an acceptable process from pork liver.

k Results expressed in micrograms per gram of powdered extract.

each unit of the anti-anemic substance. In all probability these crude preparations will be given frequently in doses of 1 to 5 cc. for non-specific liver therapy. It might be well at this point to set forth, as far as the available data will permit, just what would be included in a 5 cc. injection of highly concentrated material (15 units per cc.) as contrasted with 5 cc. of crude extract containing 2 units per cc. In making this comparison we have averaged the values for four concentrated preparations containing 15 units per cc. (Nos. 1, 2, 3 and 4, Table 1) and three crude liver extracts containing 2 units per cc. (Nos. 11, 12, 13c, Table 1). The results are as follows:

	Micrograms per 5 cc.			
	Riboflavin	Niacin	Pantothenic acid	<i>L. casei</i> factor
Concentrated . . . .	553	4842	1975	22.1
Crude . . . . .	285	4130	1816	9.7

From these figures it is evident that 5 cc. of the concentrated extract provide, in addition to 75 units of anti-anemic material, 1.9 times as much riboflavin, 1.1 times as much niacin, 1.1 times as much pantothenic acid, and 2.2 times as much *L. casei* factor, as would be obtained by the use of 5 cc. of crude extract.

The data for 3 liquid oral extracts (Nos. 17, 18, 19, Table 1) and one powder (No. 20, Table 1) for peroral use indicate the same variations in the content of the several B factors as are shown by the products for parenteral use. In general, the preparations for oral use do not compare favorably (as to B factor content) with either the crude or refined preparations for parenteral use. The average values for the 4 oral preparations are:

Micrograms per 5 cc. (Nos. 17, 18, 19, Table 1) or 5 gm. (No. 20, Table 1)			
Riboflavin	Niacin	Pantothenic acid	<i>L. casei</i> factor
650	3098	1153	13.05

**Discussion.** There is no evidence to date to indicate that any one of the well-recognized B factors is directly involved in hematopoiesis in pernicious anemia.<sup>1</sup> Sufficient time has now elapsed to establish by clinical experience that refined, concentrated liver extracts are highly effective in the control of the signs and symptoms associated with pernicious anemia. The data reported in this paper show that the crude extracts contain on the average less riboflavin, niacin, pantothenic acid and *L. casei* factor ( $B_c$ ) than do the refined, concentrated preparations. There thus appears to be little justification for the preferred use of crude liver extracts in the treatment of Addisonian pernicious anemia or as a source of the several B factors included in this report. It is possible that continued work in this field will reveal the presence of other nutritional factors which may have a quite different distribution.

**Summary.** A quantitative study of U.S.P. crude and refined liver extracts indicates that, on the average, the refined preparations contain

as much or more riboflavin, niacin, pantothenic acid and *L. casei* ( $B_c$ ) than do the crude preparations.

The writer is appreciative of the assistance rendered by our Analytical and Control Departments for the data presented in Table I.

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# PROGRESS OF MEDICAL SCIENCE

## DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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### BIOLOGIC FALSE POSITIVE REACTIONS TO THE TESTS FOR SYPHILIS

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THE Wassermann and flocculation procedures were originally regarded as specific reactions. Soon after their introduction, however, falsely positive reactions were repeatedly reported with practically all tests, not only in many non-syphilitic diseases of human beings, but in presumably normal non-syphilitic individuals as well. At first these non-specific reactions were thought to be due largely to technical errors, except in the case of leprosy and malaria. In 1926, Stokes<sup>289a</sup> reëmphasized the very proper distinction which should be drawn in all discussion of the Wassermann test between false positive results which are due to detectable errors in technique and non-specific positives due to biologic and unavoidable sources of error. He stated that no procedure had as yet been brought to light which could do away with the consequences of technical mishandling and incorrect carrying out of instructions. He predicted, however, that biologic non-specific positives could conceivably, by perfection of procedure with an increase in the specificity of the test, be entirely done away with *if instructions were exactly followed*. In 1929, under the title of "The Problem of Pseudo-Syphilis," Stokes<sup>289b</sup> made an extended report of the problem of non-specific positive reactions based on personal experience with individual cases and on the knowledge of the times. Blumenthal and Mallinckrodt-Haupt<sup>22</sup> in Jadassohn's Handbuch in 1929 presented an elaborate discussion of this problem.

Since then much attention has been paid to this subject, and it has resulted in attempts at standardization of serologic procedure through a group of serologic surveys conducted by the United States Public Health Service in coöperation with the American Society of Clinical Pathologists, in a group of important studies from the Johns Hopkins Hospital Syphilis Clinic under the direction of Dr. J. E. Moore<sup>21</sup> in the appearance of special tests and procedures to "verify" positive serologic reactions, by the revival of the use of certain "specific" antigens (spirochetal), the recommendation of certain clinical and laboratory schemes for the establishment

of the verity or falseness of a serologic reaction to the tests for syphilis, and in the appearance of a number of comprehensive reviews of the entire subject of the problem of falsely positive reactions in the serologic tests for syphilis.<sup>57, 128, 161b, 165i, 206, 211, 248, 290</sup>

The importance of this problem is further emphasized by the fact that serologic tests for syphilis are being used more and more widely on civilian and military personnel. Because of non-specific positive reactions, many individuals have been stigmatized as syphilitic and have been given unnecessary treatment on the basis of reactions disclosed by routine serologic examinations in the course of or immediately following a non-syphilitic disease. The use of serodiagnostic tests for compulsory pre-induction, pre-natal, premarital, preemployment, and other routine purposes makes the problem of false positive serologic reactions for syphilis of paramount importance.

#### Classification and Criteria of Diagnosis of False Positive Reactions.

The simplest classification of the positive serologic reactions obtained in non-syphilitic individuals is that of Stokes,<sup>289b</sup> in which false positives due to biologic and unavoidable sources of error are differentiated from false positives due to technical errors. The terminology in this field, according to Sulzberger<sup>294</sup> tends toward confusion. He claims that such terms as "false positive" or "biologic reaction" are inexact and carry erroneous implications. A positive result which is repeatable and not due to a technical error should not be called false; and the positive reaction with a syphilitic serum is a biologic positive, just as positive as a positive result with a serum of a malarial or leprous patient. He proposes the following "non-prejudicial" terms and definitions: (1) *positive syphilitic reaction* for the positive results with serums from proved syphilitics; (2) *positive non-syphilitic reaction* for the positive results with serums from patients proved to be non-syphilitic, in those instances in which the reactions cannot be attributed to technical errors; (3) *positive malarial* (or postvaccination, etc.) *reaction*, specifying the conditions to which the positive result can be proved to have been due, and (4) *false positive* when the reaction can be shown to be due to technical or other errors.

The incidence of false positive reactions will vary depending on the criteria used for the determination of a case as being false. Many reports deal with only transient positive reactions as false positive. These erroneously and automatically call syphilitic any case in which the positive reactions persist for more than a few months. It is conceivable that a patient with syphilis may also be subject to biologic false reactions. This may be the basis for some of the so-called fixed positives (seroresistance). Some indicate that a false positive reaction is one in which only one type of test gives the positive result. Repetition of tests is a *sine qua non* of diagnosis of false positive reaction. Use of social criteria leads to a situation facetiously stated by Stokes<sup>289a</sup> in 1926 as follows: (There are) "instances in which one Wassermann test will convict a laborer over his own denial, two will make a case against a banker or a railroad president, but three successive positives will scarcely convince the medical adviser of the 'guilt' of a clergyman."

Until recently there has been no real universally accepted standard for approval of serologic performance, the result being that the same specimen submitted to one laboratory, even tested with the supposedly same serologic procedure, would give grossly different results. It seems that even when performed by the originators of the tests under seemingly ideal conditions but at different times and in different places, the most dependable

and widely accepted serologic tests do not give uniform results, either as to specificity or as to sensitivity. Stokes, Beerman and Ingraham<sup>290</sup> in their review of the problem, stated that substantial agreement has been reached as the result of international and national conferences on the following points:

1. Absolute uniformity among test results on a single specimen cannot be expected.

2. Precipitation tests should be supplemented by complement fixation procedure either performed routinely or available if the result of the precipitation test is doubtful.

3. In this country at least, only five procedures are sufficiently well performed by a sufficient number of laboratories to deserve the title of "approved." These are the Kolmer Wassermann test; the Eagle, Kahn, Hinton and Kline precipitation procedures. While there is no bar advisable to the performance of other types of tests, they should be regarded in the effort to provide a dependable national serologic service, as research procedures rather than practice procedures. If additional tests are performed by any laboratory they should be a matter for supplementary report and should not be admitted to the status of "approved" until their repeated evaluation in national serologic conferences establishes their distinctive superiority.

4. The specificity of serologic tests is in general more important than their sensitivity. Specificity should be practically 100%, and in laboratory grouping and approval status, a specificity rating below 99% on 200 test specimens or 98% on 100 specimens should lead to the temporary exclusion of the test from the approved list until such time as modification reestablishes a rating for it of 100%. Sensitivity on the other hand—"an approved sensitivity rating shall not be more than 20% below that of the control laboratory in cases of late or treated syphilis and within 1% of that of the control laboratory in cases of untreated and secondary syphilis."

Unfortunately, the reported cases involving so-called false positive reactions in the literature have not been examined by such strict criteria as standardized serologic procedure would demand.

The question of sensitivity *versus* specificity of a serologic procedure must be considered in evaluating the serologic findings in a given case. Every increase in sensitiveness of a test for syphilis, that is in its ability to identify the disease in the absence of clinical signs, must be measured against the risk of pinning a partial or completely false finding upon a person who does not have the disease. It is more important, however, for practical purposes, that high specificity rather than sensitivity be accepted as the primary recommendation of a serologic procedure. Kahn<sup>146e</sup> has clearly pointed out if the ratio of syphilitic cases to non-syphilitic cases in the population is kept minimal, how much more misleading is a small error in specificity as compared with a large error in sensitivity. For example, he showed in a hypothetical case, that in 40,000 hospital admissions, with 1200 cases of treated and untreated syphilis among them, an increase of 1% in sensitivity means 12 cases of treated or untreated syphilis reported positive, while 1% increase in non-specificity means 400 non-syphilitic persons reported positive.

Another criterion which is too frequently invoked in estimating whether a serologic reaction is true or false is the strength of the reaction. False reactions are usually considered to be of low titer. For example, even Eagle<sup>71e</sup> says: "Unlike the case of animal sera, many of which give frankly positive and even high-titered diagnostic tests for syphilis in the absence

of that disease, the reactivity of normal human sera with flocculation antigens is usually only minimal in degree, requires refined techniques for its demonstration and is usually not apparent in the diagnostic tests. It is possible that the occasional human serum which gives false positive diagnostic tests contains an excess of this normal factor ordinarily present only in traces. It is equally possible that such biologic false reactions bear no relationship to the normal flocculating activity of human serum and are due to an entirely different substance."

This supposedly usually low titer of biologic false positive reactions is even considered "fortunate" by Weil.<sup>316</sup> This view leads the uncritical to conclude that one may easily differentiate a true from a false reaction merely on the basis of titer. There is no doubt that the quantitative procedure has failed as a significant differential procedure between true and biologic false reactions, but this should not be construed as a condemnation of this procedure in a scheme designed to differentiate false from true positive.

The reactions in another group of diseases must be considered, which, for practical purposes, may be called "syphilis-like" or, as Rein and Elsberg<sup>248</sup> call them, "syphiloid" diseases. These include the treponematoses such as yaws, bejel, and the disease lately admitted to this group, pinta. Strictly speaking, the reactions obtained in these diseases are true rather than false positives.

Recent compilations of the causes of false positive reactions are given by Stokes, Beerman and Ingraham,<sup>290</sup> by Rein and Elsberg<sup>248</sup> by Kolmer<sup>165i</sup> and by Eagle.<sup>71e</sup>

While it is not our intention to discuss in detail technical false positive reactions, a certain amount of attention must be given to the nature of the antigen. The most troublesome and perhaps the most frequent cause of false positive reactions in tests for syphilis is rated by Kline as the presence in the antigen emulsions themselves of adventitious materials. A full discussion of the subject of the antigen, including cardiolipin, is discussed in numerous studies.<sup>57, 115, 116, 161a, 230, 290, 316</sup>

Another confusing item which must be taken into account in dealing with serologic results is the question of zone reactions. This is the phenomenon in serologic reactions in which one observes that stronger concentrations of serum may give negative results or weaker concentrations of the serum may give strongly positive reactions. This subject has been well summarized by Eagle,<sup>71e</sup> Greene and Breazele,<sup>102</sup> Myers and Perry,<sup>218</sup> Owen, Brooks and Tucker,<sup>228</sup> and Kolmer and Lynch.<sup>170</sup>

Syphilologists are familiar with the "false negative" reactions which occur in seronegative primary syphilis, late syphilis of the heart, and neuro-axis and in treatment-resistant syphilis (Beerman<sup>14a</sup>). The whole subject of false negative reactions is reviewed by Hinrichsen,<sup>128</sup> Rein and Frank,<sup>249</sup> and by Souders.<sup>282</sup>

**Factors Involved in the Incidence of False Positive Serologic Reactions of Syphilis.** Rein and Elsberg<sup>248</sup> have well summarized a number of factors which are concerned in the investigation of false positive serologic reactions, each of which will affect the incidence of such reactions.

1. **SEROLOGIC REACTORS.** These are individuals who are more likely to develop false positive blood reactions for syphilis than others. For example, Rein and Elsberg<sup>248</sup> found that in their investigation of the smallpox vaccination group some individuals with insignificant vaccinoid reactions developed false positive serologic reactions while other individuals with the most severe vaccinia reactions remained seronegative throughout their

study. Similar observations were made in other diseases. Rein and Elsberg<sup>248</sup> were unable to determine whether these false reactions were due to:

- (a) The development of antibodies similar to syphilitic reagin.
- (b) An increase in the seroglobulins.
- (c) An altered or labile globulin fraction.
- (d) Any other change in the immunochemical mechanism.

2. TYPE OF THE NON-SYPHILITIC DISEASE. Certain diseases appear to be more likely to produce false positive serologic reactions than others. Leprosy and malaria seem to be among the worst offenders. Individuals with upper respiratory infections only occasionally develop false positive reactions while tuberculosis rarely produces such phenomena.

3. INCUBATION PERIOD FOR THE DEVELOPMENT OF FALSE POSITIVE SEROLOGIC REACTIONS. Rein and Elsberg<sup>248</sup> indicate that a definite period of time must elapse following the onset of most diseases before the false positive reactions are first detected. This period varies with different diseases and conditions. The optimal time for the detection of most false positive reactions seems to be between the 7th and 21st day of the disease.

4. NUMBER OF TESTS EMPLOYED IN THE SEROLOGIC BATTERY. The number of detectable false positive reactions will increase in proportion to the number of tests employed in the serologic battery. At the Army Medical School, Rein uses a battery of 6 tests for all serologic consultations and serologic investigations. (Kline Diagnostic, Kline Exclusion, Boerner-Jones-Lukens, Mazzini, Kahn Standard and Kolmer.) The use of this battery of tests has yielded Rein and Elsberg<sup>248</sup> a higher incidence of false positive reactions than that obtained by others in similar studies.

5. TYPES OF TESTS. The results of the serologic survey conducted by the United States Public Health Service in collaboration with the American Society of Clinical Pathologists have shown in the case of author serologist performance that certain tests give more false positive reactions than others. The incidence of false positive reactions was not necessarily directly proportional to the sensitivity of the tests, that certain diseases give fewer false positive reactions with one test than with another, and that certain tests give fewer false positive reactions with one disease and more with another disease. Rein and Elsberg<sup>248</sup> have indicated from preliminary studies that there is evidence to show that the "*serologic patterns*" of false positive reactions may vary from one disease to another according to the type of tests used. For example, individuals with primary atypical pneumonia, upper respiratory infection and smallpox vaccinations rarely develop false positive serologic reactions with a Kolmer complement fixation test, whereas the incidence is quite high with the 5 flocculation tests. There is some feeling that on the whole, because of lack of controls, the flocculation procedures are apt to yield more false positive reactions than the complement fixation tests.

6. INTERVALS OF TESTING. The incidence of false positive reactions may be increased by performing the serologic examinations at more frequent intervals. Sometimes it is necessary to do daily serologic examinations to catch the positive reactions of low titer which may tend to revert to negativity within a few days. Such transient reactions would be missed if the intervals of testing were too long.

7. DURATION OF FALSE POSITIVES. From the studies of Rein and Elsberg<sup>248</sup> at the Army Medical School, it would appear that in most instances the maximum titer of false positive reactions was obtained be-



tween the 10th and 14th day following the onset of a febrile disease or following vaccination. The length of time an individual continued to show false positive reactions appeared to depend on the degree of positivity reached on the 10th to the 14th day. The majority of serums with false positive reactions developing as a result of a limited febrile disease or smallpox vaccination became negative within 3 or 4 months. Rein and Elsberg<sup>248</sup> state that some individuals may continue to get false positive reactions for several years for no apparent reason.

*Familial Tendency to Biologic False Positive Reactions.* This has been noted rarely in some recent reports. Lindau<sup>182</sup> reported a family in which the parents and their 2 children were all serologically positive for syphilis for 1 month following an attack of bronchitis. W. Smith<sup>277</sup> encountered positive reactions in 2 young siblings 6 weeks after mumps. Zuger and Moffat<sup>328</sup> recorded an epidemiologic study of a family on 3 of whose 4 members false positive serologic reactions to the tests for syphilis were obtained simultaneously. These tests were traced as presumably originating from a mild upper respiratory infection. Among a small number of contacts exposed to the same infection as the members of this family, there was evidence that suggested that they were immunologically similarly affected.

**Syphilitic Reagin in Normal and Apparently Non-syphilitic Human Blood and in Animal Blood.** It has been shown that the serum of many apparently normal persons may show measurable or even important amounts of the reagin or reagin-like substances responsible for biological false positive reactions.<sup>272</sup> It has also been demonstrated that the serum of a number of animals gives, in varying percentages, positive results to serologic tests for syphilis even though the animals are known to be demonstrably incapable of inoculation with the disease. This latter fact should not, as Kemp, Fitzgerald and Shepherd<sup>157</sup> have indicated, be regarded as evidence of unreliability of serologic tests for syphilis in man. Many observers have shown that complement fixation techniques can be so modified, for example, that they are always negative in non-syphilitic rabbits and regularly positive at the height of the infection in syphilitic rabbits, notwithstanding the fact that a certain proportion of rabbit serums react positively to complement fixation tests for syphilitic reagin under certain modifications of technique. The whole subject of positive serologic reactions for syphilis in animals is well reviewed by a number of authors.<sup>51,85,104,105,157,252,273,274</sup> The cause of this positive reaction in animals is not known. The absence of heterophil antibodies in the cow, as demonstrated by Greene and Harding,<sup>104</sup> indicates that the substance which gives rise to positive Kline reactions is different from that present in the serums of patients suffering from infectious mononucleosis.

In 1931 Malloy and Kahn<sup>195</sup> succeeded in showing that when normal serum is mixed with standard Kahn antigen, microscopic aggregates gradually form. They were able to establish quantitative relations between the areas of aggregation developed during various periods of exposure for normal serums and for syphilitic serums mixed with a standard and a sensitized Kahn antigen as used in the Kahn presumptive test. As the authors put it, "It appears that the difference between non-syphilitic and syphilitic serum is one of degree rather than of kind; that it is quantitative rather than qualitative." What occurs in syphilis is the increase of a lipoid aggregating quality possessed nonetheless even by non-syphilitic serums. In 1942 Kahn and his associates<sup>147</sup> showed that the number of non-specific sensitivities of a serodiagnostic test for syphilis can be readily

increased by various modifications of the test. The use of excessively sensitive antigens may result in as high as 40 % of false reactions. The use of such antigens combined with the performance of the tests at 1° C. may result in about 89 % of false positive reactions. If, in addition, unheated serums are employed (instead of serums heated at 56° C. for 30 minutes) the non-specific sensitivity may approach 100 %.

Pierce and Breazeale<sup>239</sup> summarize experiments with plant saps and adsorbents such as calcium and sodium zeolite in which they find evidence that "reagin" is a divalent sodium or magnesium cation participating in a base exchange reaction. The beef heart antigen acts as a zeolite in producing a floc. The work is as yet unconfirmed. Barnes and his co-workers<sup>7</sup> have suggested from their work that even diet may play a part in non-specific reactions, since in some cases positive reactions have become negative promptly following the use of a meat-free, milk-free, abundant liquid diet. The effect of alcohol ingestion on serologic reactions is one debated for a long time. Brittingham and Rosen<sup>33</sup> thought the influence of this agent was overestimated. It had no apparent effect on various serologic tests in patients with untreated syphilis. In 1935 Hoversen, Peterson and Sackett<sup>132</sup> even claimed that meteorologic variations affect the outcome of the serologic tests for syphilis. This has been denied by Kelley and Short<sup>155</sup> and, although Greval<sup>107</sup> noted such a seasonal variation, he felt that it was due to defects in the complement. Schreus and Foerster,<sup>268</sup> as well as Barnett, Jones and Kulchar<sup>8</sup> devised methods and accomplished the demonstration of syphilitic reagin present even in the serums of non-syphilitic individuals. Later Barnett, Kulchar and Jones<sup>9</sup> found, in confirmation of the pioneer study of Strickler, Munson and Sidlick<sup>291</sup> that an injection of neoarsphenamine to non-syphilitic subjects caused a definite increase in reagin-like substance in their serums. Lund,<sup>191</sup> using a method of flocculation employing maximal serum proportions with secondary recovery of antigen, succeeded in demonstrating the presence of reagin in normal serums. Sherwood, Bond and Canuteson<sup>272</sup> demonstrated a positively reacting substance in the blood of 13 of 1017 healthy students. In an elaborately conducted and controlled survey of 40,545 students' serums Eagle<sup>71</sup> estimated the incidence of one false positive reactor in every 1125 students as the probable normal for the biologic false positive. Statistically corrected for other considerations, this proportion fell to 1 in every 4000 persons tested. In a similar study, Greene, Breazeale and Andes,<sup>103</sup> using the Kahn and one of a number of other flocculation procedures, found 1.66 % positive or doubtful non-specific reactions among a carefully studied group of 5000 college students. Mohr, Moore and Eagle<sup>206</sup> have recently reported 9 normal persons yielding biologic non-specific reactions.

Among hospitalized patients, various estimates of the incidence of false positive reactions have been given. Crawford and Ray report 0.42 %, <sup>54</sup> Clifton and Heinz,<sup>48</sup> 1.46 % (children); Hill,<sup>127</sup> 0.14 % repeatedly positive and became negative within 1 week to 9 months without treatment; Forssman,<sup>87</sup> 0.13 %; Eldh,<sup>76</sup> 0.25 %; Krag,<sup>173</sup> 0.027 %, and Krag and Lønberg,<sup>174</sup> 0.04 %. Davis,<sup>57</sup> who has compiled the statistics from the literature, feels that the Scandinavian authors have reported so low an incidence because of the stringent criteria used. Lynch,<sup>192</sup> in an interesting report, stated that "even in good laboratories the number of doubtful or conflicting reports may equal the number of significant strongly positive reactions." On a series of 2764 patients recently admitted to the University of Minnesota Hospital, "the incidence of subsequently diagnosed syphilis

was nearly 1.5 %, but misleading serologic reports were obtained in 2 % of the whole group. When there is clinical evidence of syphilis, it is obvious that partially positive serologic reports are probably significant, but in the absence of other demonstrable evidence one must look askance at reports of 1, 2, or 3 reactions even on multiple specimens. One must also be suspicious of falsity when on the same specimen positive reactions by one technique are accompanied by negative reactions to another."

The daily variation of reagin content of syphilitic serum has long been regarded as a basis for the fluctuating and alternating positive and negative reactions in serial tests on syphilitic and non-syphilitic individuals.<sup>52,101,289c,301</sup> If the work of Mohr and Smith<sup>208</sup> is confirmed, a large part of this clinically recognized daily variation will have to be assigned to the category of technical rather than biologic error or variability. Mohr and Smith<sup>208</sup> showed by collecting and freezing a series of sera that the variability in reaction as between individual successive specimens practically disappears when a series of frozen specimens is examined at one and the same time. Daily variability in serologic results is probably the result primarily of daily fluctuations of the sensitivity of the tests employed. (Cf. Stern,<sup>287</sup> Haller,<sup>114</sup> Meirowsky,<sup>202</sup> Meier,<sup>201</sup> Eagle,<sup>71e</sup>.) This periodic variability of serologic outcome must not be forgotten in evaluation of clinical material. Attempts have been made to produce false positive Wassermann reactions artificially by the addition of certain chemicals to negative serums. These reactions, strictly speaking, cannot be classed as biologic, but may throw some light on the causal mechanism of biologic false positives. Owen, Brooks and Tucker<sup>228</sup> tried cholesterol, potassium, calcium, tannic acid (in bottle corks). None of these produced a positive reaction. Tannic acid or acetic acid added directly to negative serums did produce a positive reaction. Eagle,<sup>71a</sup> in an earlier study, was unable to make an originally negative human serum Wassermann-positive by physical or chemical treatment. Breazeale,<sup>30</sup> in a series of papers, showed that certain physical manipulations, *e. g.*, ultraviolet light, diathermy, and so forth, could change serum reactivity. Rytz,<sup>258a</sup> in 1935, was able to obtain strongly positive Wassermann and flocculation reactions in rabbits by injecting intravenously the flocculate obtained from human syphilitic serum. Becker<sup>13</sup> confirmed this phenomenon in rabbits and showed, in addition, that this human syphilitic flocculate was antigenic because 10 times as much flocculate was obtained as the amount injected into the rabbit.

### Diseases and Other Conditions Responsible for Biologic False Positive Reactions.

**Yaws, Bejel and Pinta.** These 3 treponematoses described as "syphilis-like," "syphiloid" or actually syphilis, are all caused by organisms indistinguishable from *Spirochæta pallida*. In the strict sense, positive serologic reactions occurring in these diseases should not be considered as false, but true positives. In view of the fact that they are of importance mainly in the locales where they are endemic, and the fact that they respond to antisiphilitic therapy, differentiation from venereal syphilis is of little practical importance. The serologic findings in bejel have been reviewed by Hudson,<sup>134</sup> those in pinta by Beerman,<sup>14b</sup> and those in yaws by Mal-taner.<sup>195</sup>

**Leprosy.** A survey of the literature on the incidence of biologic false positive reactions in leprosy reveals that there is a wide variety of figures,

but the trend is generally toward a high percentage. Some believe that this may be due to the occurrence of a high proportion of syphilis and yaws among lepers (Hazen *et al.*<sup>119</sup>). Howard Fox<sup>89</sup> was one of the first in this country to point out that a positive Wassermann reaction is frequently obtained in cases of leprosy without history or symptoms of syphilis. Of course, estimates of the occurrence of positive reactions in patients with this disease are conditioned by the type of test employed. For example, Kolmer and Denny,<sup>166</sup> in 1923, reported that in 123 cases studied with the old Wassermann technique, apparently false positive reactions occurred in 7.2 % of patients with leprosy, but that the Kolmer modification did not give false positive reactions in leprosy. Yagle and Kolmer<sup>327</sup> applied the Kahn test to 28 patients with leprosy and concluded that in leprosy uncomplicated with syphilis, the Kahn test gave negative reactions. In the United States, the 1934 evaluation study of serologic tests<sup>55</sup> showed that in 50 lepers the Kolmer test gave 64 % false reactions, the Kahn test 60 %, the Eagle flocculation 72 %, the Kline test 66 % and the Hinton test 40 %. When clinical studies to exclude syphilis and repeated serologic tests were made, only 15 patients (30 %) had positive or doubtful reactions to all tests, 8 % had negative reactions and 62 % showed discordant reactions with the different tests.<sup>119</sup> Some authors claim that there is no relationship between the phase of leprosy and the serologic reactions.<sup>67</sup> Other authors<sup>3, 80, 130, 185, 212, 236</sup> have related the higher incidence of positive reactions to certain aspects of leprosy, especially the mixed or lepromatous cases. Badger<sup>5</sup> found more positive cases among women.

These considerations, therefore, leave little wonder that various authors have obtained such a variety of results from the application of serologic tests to leprosy.<sup>5, 29, 80, 119, 130, 137, 185, 212, 215, 224, 226, 248, 262, 275, 283, 305, 323</sup>

In order to differentiate true from biologic false serologic reactions in lepers, Capelli<sup>39</sup> performed complement fixation tests on the serums of 24 leprous patients using Gaechtgen's phenolized culture<sup>94</sup> of *Spirochæta pallida* (palligen) as antigen, and compared the results with those obtained with the Wassermann procedure and the Meinicke flocculation test on the same serums. He reported that with the spirochetal test none of the serums gave a 4 or 3+ reaction except in 1 patient who was considered to be syphilitic. There were partially positive (1 or 2+) reactions with 22 % and negative reactions with 78 % of the serums. The Wassermann reactions were positive with 66 %, partial with 17 %, and negative with 39 % of the serums. On the basis of these results, Patrick and Wolfe<sup>236</sup> reviewed cases of leprosy and concluded that when examined with the spirochetal complement fixation test, the serums of non-syphilitic leprous patients show a tendency toward falsely positive results, although to a lesser extent than with the Wassermann and Kahn tests. Eagle and his associates<sup>73</sup> examined a group of lepers' blood and cerebrospinal fluid with the spirochetal complement fixation test and concluded that in partial confirmation of the work of Capelli, this procedure makes it possible to identify as biologic false positive reactions most of the positive Wassermann and flocculation reactions caused by leprosy in the apparent absence of syphilitic infection. Kolmer<sup>165a</sup> on the other hand, stated that the spirochetal antigens give a particularly high percentage of non-specific or falsely positive complement fixation reactions in the blood from patients with leprosy and malaria, just as tissue or lipoidal antigens yield a high percentage of positive Wassermann and flocculation reactions in the blood of patients with these diseases. The Kahn verification test has also been of little if any value in identifying true from false reactions in leprosy.<sup>46</sup>

**Malaria.** Much has been written about the ability of malaria to provoke biologic false positive reactions with the various serodiagnostic tests. From flat denial of any effect,<sup>165b,c,183,184,264,276</sup> the estimates have ranged to the statement that by means of serially repeated tests<sup>79,160,176</sup> 90 to 100% of malarial patients at some time in the course of the disease had biologic false positive serologic reactions for syphilis. The more frequently the tests are made, the higher the percentage of positive reactions. The reactions in the cerebrospinal fluid do not parallel the blood changes.<sup>176</sup> The difference of opinion as to the incidence of these false positive reactions is probably due to the inability to exclude the coëxistence of syphilis and other syphilis-like diseases such as yaws which usually gives positive serologic reactions. Most of the positive serologic reactions in malaria occur between the 7th and 21st days of the malarial seizure. Kitchen, Webb and Kupper<sup>160</sup> found that the highest percentage of positive reactions occurred during the period 15 to 21 days after the last previous paroxysm. The greatest number occurred between the 15th to the 21st day after inoculation of induced malaria and most of the positive reactions had disappeared by the 4th week.<sup>36</sup> Kitchen and his co-workers<sup>160</sup> noted that *Plasmodium vivax* infections gave more positive reactions than *Plasmodium falciparum*. Hazen and his co-workers<sup>120</sup> found that the highest proportion of biologic false positive reactions occurred in females. Eagle, Mays, Hogan and Burney<sup>74</sup> stated that the spirochetal complement fixation test was of little value in the serologic differentiation of syphilis and malaria. Kolmer<sup>165g,h</sup> concurs in this view, since spirochetal antigens give a particularly high percentage of non-specific reactions in malaria just as tissue or lipoidal antigens. The Kahn verification test did not always give a consistent reaction in patients with malaria at the hands of Chargin and Rein<sup>46</sup> but DeGroat<sup>63</sup> believed his study showed that the verification test can be employed as an aid in establishing the differential diagnosis of malaria and syphilis. Rosenberg,<sup>255</sup> from his study of this problem, concluded that the Hinton flocculation test for syphilis yields the smallest proportion of falsely positive reactions in malaria of any of the widely accepted serologic techniques. The pattern of positivity in malaria, *i. e.*, positive Kahn and Mazzini reactions, doubtful Kolmer and Kline reactions and negative Eagle and Hinton reactions, can usually be differentiated from that of syphilis. Persistence of positivity by any test beyond 6 weeks in the absence of continued evidence of malaria should arouse suspicion of syphilis.

There is no established explanation for the cause of the false positive reaction in malaria. Eller<sup>77</sup> pointed out that the nature and the regularity of appearance of a positive Wassermann reaction in certain stages of inoculation malaria leads to the assumption that the processes which bring about a positive serologic reaction are similar to those in syphilis. Fischer and Gunsberger<sup>84</sup> believed that the positive Wassermann reaction was due to specific antibodies against erythrocyte lipoids. Among 28 serums obtained from malaria patients, there were 21 with definite to completely positive complement fixation with erythrocyte extract (malaria antigen). With few exceptions, 500 Wassermann negative serums from healthy persons and patients reacted negatively. There were some among 60 Wassermann positive syphilitic serums which also reacted with the erythrocyte extract, but these could be differentiated from those of malaria patients by considering the quantitative reaction to erythrocyte extract and Wassermann extracts. When both reactions are tested for simultaneously, the authors believe malaria may be differentiated from syphilis.

For the interested reader, there are numerous reports on the influence of malarial infections on the serologic reactions.<sup>36,55,56,60,63,83,106,118,124,160,203,221-222,233,234,235,248,255,322,398</sup>

**Pneumonia and Respiratory Infections.** There has recently been a rising interest and appreciation in this country and abroad of the importance of respiratory infections and pneumonia as a cause of biologic false positive serologic reactions. Eldh<sup>76</sup> in 1932 made serologic studies on 20,798 medical patients and found that 52 of them had probable false positive reactions. Twenty-six of these 52 patients had pulmonary disease and there were 10 cases of pneumonia (out of 1014 cases of the disease), 6 emphysema, 7 tuberculosis and 3 influenza (out of 548 cases so diagnosed). Other authors, especially from Scandinavia, have reported cases of respiratory infections with transient positive serologic reactions. Krag and Lønberg<sup>173,174</sup> of the Danish Serum Institute, in testing the serums of 120,000 presumably non-syphilitic patients, uncovered 53 patients (0.04%) with biologic false positive serologic reactions for syphilis. Of the 53, 60% were from patients with respiratory infections. Boas and Neergaard<sup>23</sup> reported on 1 case of bronchopneumonia and 2 with bronchitis with false positive reactions. Kissmeyer,<sup>159</sup> who reported 10 cases with biologic false positive serologic reactions for syphilis, had 2 patients with pneumonia among them. Similar reports of false reactions in pneumonia were reported by Forssman,<sup>87</sup> Krag,<sup>173</sup> Munch-Anderson,<sup>216</sup> Gigante,<sup>96</sup> and Jahnel.<sup>139</sup> Stryjecki stated in 1938<sup>292</sup> that about 5% of patients with pneumonia have biologic false serologic reactions for syphilis. Lindau<sup>182</sup> noted 10 transient positive cases of respiratory infection. Among his cases were 4 members of a family of 5 suffering from bronchitis. Clifton and Heinz,<sup>48</sup> using the Kolmer Wassermann, the Kahn and the Eagle tests in a survey of prenatal syphilis in a hospital for sick children, found an incidence of 1.46% of false positive reactions, a majority of which were obtained from patients with respiratory infections. Mohr, Moore and Eagle<sup>206</sup> found a rather high incidence of respiratory disease among their patients with false positive reactions. They also reported 2 patients with sore throats and 1 of labyrinthitis of unknown cause, in all of whom false positive serologic reactions appeared. Allen Hill<sup>127</sup> noted 242 non-specific reactions (positive and doubtful) among 26,700 Hinton and Davies-Hinton microflocculation tests from the records of the in-patient and out-patient services of the Infants' and Children's Hospitals of Boston. Of these tests, 114 obtained from 37 patients represent false positive and false doubtful reactions which were proved. The remaining 128 tests are single positive or doubtful results which may be either non-specific reactions or the consequence of laboratory or clerical error. Respiratory infections in particular, and acute infections in general, make up a major portion of the non-specific reactions noted in Hill's study. Bridgeman and Jacobson<sup>32</sup> also reported such cases in children.

In 1936 Fanconi<sup>81</sup> reported a clinical picture for which he suggested the name "pseudoluetic, subacute, hilifugal bronchopneumonia of poor children." This was associated with false positive reactions to the serologic tests for syphilis. In 1941, Hegglin and Grumbach<sup>122</sup> published observations on a similar disease in adults under the designation, "Das Wassermann-positive Lungeninfiltrat." They studied, among other things, the frequency of non-specific Wassermann reactions in pneumonia, bronchopneumonia, and pulmonary tuberculosis in the medical clinic in Zurich in the years 1938 to 1940. Among 680 pneumonia and bronchopneumonia patients there were 19 with non-specific serologic reactions (2.8%), and

among 403 cases of pulmonary tuberculosis 13 (3.2%). The authors called attention to the fact that these were cases with a weak or doubtful Wassermann reaction, or cases where only the Kahn or Citochol reaction was observed in only 1 case, died shortly thereafter, and no evidence for syphilis could be found at autopsy. In the same year, Benedikt<sup>17</sup> encountered 7 definite and 1 possible additional cases of this "pseudoluetic pneumonia" in the Children's Hospital of the University of Zurich. Grumbach<sup>109</sup> found *Hæmophilus Pfeifferi* as the sole organism in the sputums of 6 cases. In an animal study, it appeared that the Wassermann, Kahn and Citochol flocculation negative rabbits by immunization with the influenza bacillus of Pfeiffer became Wassermann and flocculation positive, and the strength of the agglutination titer went parallel with the intensity of the Wassermann reaction. This was felt to indicate that the influenza bacillus, like alcoholic tissue extracts, possesses a fraction like *Treponema pallidum* which calls out a positive reaction for syphilis. However, 42 cases (25 pneumonia, 13 grippe, 4 "grippe-pneumonia") with positive agglutination for influenza bacillus, yielded negative Wassermann reactions. Also, in 2 cases of influenza (Pfeiffer) meningitis, the Wassermann and flocculation reactions were negative.

While there is no definite reason to call these cases from Switzerland virus pneumonia, the symptomatology, as described by Fanconi,<sup>81</sup> are very similar to the so-called "primary atypical pneumonia of unknown etiology." In reports of known atypical pneumonia, there has been suggestion, though scant mention, of the possibility of biologic false positive reactions in tests for syphilis.<sup>66,162</sup> Major Charles R. Rein, Chief of the Division of Serology, Army Medical School, in a personal communication to Kolmer<sup>165</sup> stated that 10 cases in 50 have shown false positive reactions after the 12th day of the disease, the majority disappearing or reacting negatively in 2 to 6 months. In a later communication, Rein and Elsborg<sup>248</sup> studied a group of 72 patients with primary atypical pneumonia with radiologic evidence of pulmonary involvement. These patients were subjected to serologic examination as soon as possible after hospitalization. In most of the patients the first symptoms were malaise, cough and elevation of temperature 5 to 10 days prior to hospitalization. Weekly repetition of the serologic tests was attempted, but in 42 (58.3%) only a single serologic examination was possible. Of the 72 patients, 17 (23.6%) gave positive serologic reactions with 2 or more tests in the Army serodiagnostic battery. Ten patients gave low titered positive reactions, while 7 of them gave strongly positive serologic reactions. The majority of these individuals became seronegative within 3 months after the onset of the illness.

Cold agglutinin tests were also done on the serums, from these patients, but there did not appear to be any direct correlation between the false positive serologic reactions and the positive cold agglutinations.

Serums of 36 patients in this group were also subjected to a complement fixation test for psittacosis and here, again, there was no relationship between the false positive reactions for syphilis and the false positive psittacosis reactions.

Of 79 patients with miscellaneous upper respiratory infections, including influenza, bronchitis and lobar pneumonia, similarly investigated, 20.2% gave false positive serologic reactions for syphilis and positive cold agglutination tests were much lower in titer than those obtained in the primary atypical pneumonia group.

Loveman<sup>188</sup> felt that in his 100 cases of false positive serologic reactions for syphilis, Army immunization played a greater rôle than did upper

respiratory infections. Davis,<sup>57</sup> in his exhaustive review, calls attention to the interesting fact that Gigante<sup>96</sup> suggested that false positive reactions in pneumonia might be related to the herpes virus according to Koch's concept but "such an explanation appears unlikely since the activating herpes in pneumonia is extremely common." He also calls attention to the fact that while false positive reactions may occur in various upper respiratory diseases, undoubtedly some of the reported so-called upper respiratory infection cases may have been undiagnosed infectious mononucleosis.

**Infectious Mononucleosis.** Infectious mononucleosis (glandular fever) is a disease which has aroused much interest in the internist. To the syphilologist, it is of special importance because the symptomatology, so much like secondary syphilis<sup>187,261</sup> may be accompanied by positive reactions in the serologic tests for syphilis. This association of biologic false positive reactions and infectious mononucleosis has been the subject of special reports<sup>20,117,154,167,204,261,263,315</sup> and has been deemed deserving of mention in general articles on infectious mononucleosis,<sup>20,38,88,97,113,135,231-232,241,243,310,312,317</sup> or papers devoted to discussion of biologic false positive reactions.<sup>57,165i</sup> Others have, however, denied that this disease may be associated with false serologic reactions. Löhe and Rosenfeld<sup>187</sup> were apparently the first to note the fact that a transitory positive Wassermann reaction may sometimes appear during the course of infectious mononucleosis ("monozytenangina"). Parkes-Weber,<sup>231</sup> however, was actually first to call attention definitely to the fact that temporarily positive serologic reactions for syphilis may occur in glandular fever.

Attempts at estimating the actual incidence of false positive serologic reactions in this condition have been made by various investigators. Sadusk<sup>261</sup> felt that the reports suitable for analysis would indicate that approximately 15% of such patients present a temporarily positive syphilis serology during the course of their illness without any history of manifest evidence of syphilis, though it is possible that a much higher incidence may be found in future studies by the performance of serologic tests more regularly and persistently. For example, in 1939, he found 8% of 37 cases in which 1 or more serologic tests for syphilis were applied, but in 1941 he found 13% of 45 patients. This increase was due to the fact that in the additional 8 patients the serologic tests for syphilis had been repeated at regular intervals. Other estimates of the incidence of positive serologic reactions in this disease are: Gooding,<sup>97</sup> 60% of 27 cases; Bernstein,<sup>20</sup> 16% of 37 cases. Kolmer, Ginsburg and Lynch<sup>167</sup> collected 191 cases from the literature and found an incidence of 20.9%. Their own series of 18 patients, 16 of whom had only 1 test, gave completely negative reactions to the Kolmer quantitative complement fixation and Kahn standard flocculation tests, but the Kline diagnostic test gave 1 positive and 1 doubtfully positive reaction in the group. In a later review, Kolmer<sup>165i</sup> showed that the incidence of reactions reported by various investigators has varied all the way from none<sup>204,205</sup> to 100%, with an average of 7.3% doubtful or positive complement fixation reactions in 202 cases and 9.6% doubtful or positive flocculation reactions in 157 patients.

Usually the false reaction appears during the 2nd week of the disease and, according to Sadusk<sup>261</sup> may rarely appear during the latter part of the 1st week. It usually becomes negative within 2 weeks, but may persist longer (2 months;<sup>261</sup> 3 months<sup>170</sup>). The titers of the reactions in infectious mononucleosis are usually lower than those in secondary syphilis.

Various explanations have been offered for the occurrence of the false



serologic reactions in infectious mononucleosis. Nonetheless, the mechanism is actually unknown. Werlin, Dolgopol and Stern<sup>317</sup> believed there was no correlation between the titer of the heterophil antibody reaction and this false positive tendency (Cf. Bernstein<sup>290</sup>). Warren<sup>312</sup> felt that falsely positive Wassermann, Kahn and Eagle reactions were frequent in infectious mononucleosis and proposed two mechanisms for these findings: (1) the antibodies may be those normally present or previously acquired in some manner; (2) the chemical and spatial structure of the antigens of various diseases giving non-specific reactions (typhoid, paratyphoid, undulant fever) and infectious mononucleosis may be very closely related.

It was early stated that reagin, the substance responsible for positive syphilis serologic reactions, was not responsible for the occurrence of the positive Wassermann reaction in infectious mononucleosis. This was based on the occurrence of negative Kahn reactions. This argument is invalidated by the consequent observation of the simultaneous occurrence of both positive Kahn and Wassermann reactions in a patient. Furthermore, Kaufman<sup>154</sup> had among his patients with infectious mononucleosis, 2 seronegative treated congenital syphilitics. The Wassermann reaction did not revert to positive in either during the course of the infectious mononucleosis. Sadusk<sup>261</sup> noted two peculiarities of false positive serology in infectious mononucleosis and suggests that whatever is responsible for the positive reactions is not reagin. These peculiarities are negative flocculation and positive Wassermann, and in 1 case the Wassermann reaction was more strongly positive with the alcoholic than with the cholesterolized antigen. Saphir<sup>263</sup> has invoked the idea of a change in the blood proteins (Cf. lymphogranuloma venereum) as the responsive factor. Sadusk's<sup>261</sup> study of 2 patients did not sustain this view. It has been suggested that these reactions may be due to a reaction between heterophil antibody in the serum and heterophil antigen in the alcoholic extracts of mammalian tissues employed in these tests.<sup>117,285</sup> This view is considered untenable by Kolmer<sup>167</sup> and his associates on the basis that the positive reactions should occur only in the complement fixation and flocculation tests employing extracts of the tissues of certain animals known to contain heterophil antigen, whereas negative reactions should occur in tests employing extracts of tissues of animals regarded as free of heterophil antigen.<sup>38</sup> The Kolmer antigen, for example, is prepared of beef heart (1 of the animals known to be free of heterophil antibodies). While Kolmer, Ginsberg and Lynch<sup>167</sup> as well as Mills and Jahn<sup>204</sup> found infectious mononucleosis to give consistently negative results, positive results to flocculation tests performed with beef heart antigen have been encountered by various authors.

Kolmer<sup>165d</sup> carried out studies to determine whether or not *Listerella monocytogenes* could produce in rabbits the reagin or antibody-like substance responsible for the Wassermann and various flocculation reactions which occur in syphilis. Intravenous immunization of rabbits with living and heat-killed avirulent strains did not produce complement fixing or flocculating reagins for antigens commonly used in the serodiagnosis of syphilis, and also did not produce agglutinin for sheep erythrocytes in the immunization of rabbits. Davis,<sup>57</sup> in his masterful review, cited the following conclusive evidence against the relation of the heterophil antibody to sheep cells to biologic false positivity: (1) flocculation tests are also frequently positive, although antish sheep cell hemolysin plays no rôle in these; (2) there is no correlation between the heterophil antibody titer and serologic tests;<sup>20</sup> and (3) absorption of a few such sera with sheep cells has

removed the heterophil antibody without appreciably affecting the serologic tests.<sup>20,117,167</sup>

**Vaccination and Immunization.** Because of the serious implications of positive serologic reactions, true or false, in military personnel, the fact that routine procedures such as vaccination and other immunization procedures may induce biologic false positive reactions to blood tests for syphilis makes it necessary to ascertain the extent and character of this phenomenon.

In 1940 Barnard<sup>6</sup> first modestly reported a patient whose blood showed a series of positive reactions for syphilis following successful vaccination for variola. The positive reactions persisted for more than a month. Some doubt has been raised that vaccinia caused the positive reactions in this case because the "primary take" did not appear until nearly 3 weeks after vaccination, but the evidence submitted was reasonably conclusive that vaccinia was the causative factor. Barnard<sup>6</sup> also mentioned that Giordano discussed a similar case in 1935. In 1941 Giordano also informally reported to Lynch and his co-workers<sup>193</sup> that he had observed another person who had a false positive serologic reaction associated with vaccinia. In each case the strongly positive reaction gradually changed to negative within 45 days. In 1940 Bay and Sankstone<sup>10</sup> reported that because they had examined 100 serologically negative persons both before and after vaccination, with negative results, they concluded vaccination was not an important cause of false positive reactions. Mohr, Moore and Eagle<sup>206</sup> also reported a case among their patients yielding false positive reactions. Thomas and Garrity<sup>302</sup> also investigated this problem and in 2 reports which include 20,000 Kahn tests made on recruits entering the Naval Training Station, San Deigo, between July 1939 and January 1941. All the tests were run by the same technicians. In the entire series of 20,000 there were 73 (0.365%)\* positive initial Kahn reactions, of which 32 (0.16%) proved to be false positives and 41 (0.205%) were persistently positive. Of the 41 positive cases, 10 were definitely believed to have acquired syphilis, 3 to have congenital syphilis; 20 probably had the disease, and 8 were exceedingly doubtful. Of this group, of positive cases, 65% had had promiscuous relations with prostitutes, 28% had had few sexual contacts, and 7% denied sexual intercourse. The findings suggest a definite relationship between cowpox vaccination and the false positive test. In the first 10,000 tests the blood was taken after vaccination; in this group there were 26 false positives. In the second 10,000 the blood was taken before vaccination and there were only 6 false positives. One particular case in the second group is cited. This recruit had a negative Kahn reaction on arrival and 3 weeks after vaccination a strong positive which persisted for 3 weeks, since which time it has remained negative. No relationship between antityphoid inoculation and the false positive Kahn test could be found. Several recruits from the Southern Gulf States developed clinical malaria after their arrival, and all of these had positive Kahn tests at some time during their treatment. The tests which were found to be falsely positive became negative within a period of 4 weeks.

Lynch, Boynton and Kimball<sup>193</sup> demonstrated conclusively that small-pox vaccination was a frequent cause of false positive reactions. In a careful and well-controlled study of 263 persons with a primary vaccinia they obtained an incidence of 16% positive individuals by one or more

\* This figure corresponds to that obtained by Barnard<sup>6</sup> who had 4 positive reactions among 1116 male college students of about the same age and geographic distribution of the naval recruits.

of the Kolmer, Kline, Hinton and Mazzini tests. The intensity of the reactions varied from doubtful to 4+ and in most cases they appeared in 2 weeks and remained positive for 2 months. Several of the positive reactions persisted for 4 to 5 months. Individuals with accelerated or immune reactions were not included in this study. The Kahn verification reaction was of the syphilitic type in the only case in this series in which this procedure was performed. The authors felt that the recognition of the highest possible number of false positive reactions would require the performance of tests on specimens collected more frequently through the period from 2 to 6 weeks after vaccination. This procedure might have yielded a different figure than the 16% recorded.

Arthur and Hale<sup>4</sup> found that 14 of 94 soldiers (14.8%) gave a temporary false positive reaction after smallpox vaccination. These same men also had been recently vaccinated against typhoid fever, tetanus, smallpox and yellow fever. These authors believed that the false reactions were the result of the combined inoculations of the routine Army immunizations. Lubitz,<sup>190</sup> in 1943, found titers as high as in syphilis in individuals vaccinated, but the reactions disappeared quickly (2 to 17 days) on storage at 4° C. They were negative 14 to 104 days after vaccination. Positive reactors failed to give the heterophil antibody test. In another study of 100 unhospitalized individuals with a primary smallpox vaccination he obtained 13% positive reactions to 1 or more tests.

Favorite,<sup>82a</sup> in 1943, had an opportunity to make a study similar to that of Lynch and his co-workers.<sup>193</sup> Importation of a case of smallpox near the Philadelphia area led to mass vaccination of approximately 1,000,000 persons. He selected a group of 202 individuals who had had a serologic test for syphilis within a reasonable time previous to vaccination. Their ages ranged from 3 weeks to 84 years and over half of them were between 20 and 30 years of age, and consisted mostly of medical students and nurses. Of these individuals, 44 developed a primary cutaneous (non-immune) reaction at the site of inoculation, 134 developed a local accelerated (vaccinoid) form, and 24 were immune. Of the 202 individuals on whom a single blood examination was performed 19 were found to be positive by 1 or more of the Kolmer simplified complement fixation tests, the Kahn and Mazzini flocculation tests. They were examined from 10 to 57 days following vaccination, but 93.6% were done before the 43rd day. Of 24 persons who gave a negative reaction 14 days after vaccination and were reexamined 14 days later (1 month after vaccination), 4 were now positive. Favorite<sup>82</sup> believed more positives would have been found if the entire group had been examined in a similar manner. In all, 24 of 202 (11.8%) gave a false positive reaction for syphilis. The reactions were about equally divided between the non-immune and accelerated groups. Since none occurred in the immune, the percentage would have been higher if this group were excluded. The reactions were usually 2+ or less (negative or doubtful) but 22.4% were 3+ or stronger. Only 8 were still positive at the end of 60 days; 4 were weakly positive in 80 days and 2 persisted for 100 days. By 120 days all were negative.

In 1944 Favorite<sup>82b</sup> was able to make a second study of this problem. The entire student body of a medical school was vaccinated against smallpox in January 1943. Subsequently, a new freshman class was enrolled, leaving three-fourths with a recent vaccination. Six months later the students were again subjected to vaccination, not only to smallpox, but to typhoid, paratyphoid fever and tetanus. Since smallpox vaccination was given after the administration of typhoid vaccine and 2 injections of

tetanus toxoid, an opportunity was offered to determine just what rôle such immunization played in the production of false positive reactions for syphilis. It also offered additional data for the continued study of smallpox as a cause of false positive reactions. Other factors were also studied.

The second group included 323 men between the ages of 21 and 30 years, three-fourths of whom were vaccinated for smallpox 6 months previously. Following a preliminary blood test, they were revaccinated. Six individuals developed a primary cutaneous (non-immune) reaction, 71 developed an accelerated (vaccinoid) form, and 246 were immune. One month after the date of vaccination, a blood specimen was obtained and examined with the Kolmer, Kahn and Mazzini tests. No opportunity was offered for more frequent and prolonged observations. The results of the study showed that smallpox (vaccinia) vaccination followed by an accelerated or primary (non-immune) cutaneous response causes at least 11 to 16%. An immune response to smallpox vaccination can be disregarded as a significant cause of a false positive reaction.

The false positive serologic reactions for syphilis are transitory, appearing within 2 weeks of the date of vaccination and disappearing in most instances, within 2 months or persisting occasionally as long as 4 months. Typhoid (T.A.B.) and tetanus toxoid immunizations have no significant bearing on the production of false positive serologic reactions for syphilis. Favorite's<sup>82</sup> study also suggested (a) that recently vaccinated individuals who gave a positive serologic reaction do not have a reactivation of their positive reactions following typhoid and tetanus immunizations 5 months later, and (b) individuals with a false positive serologic reaction, when revaccinated for smallpox within 7 months, may again present a weak serologic false positive response for syphilis, even though the second vaccinia reaction is of the immune type. Positive serums stored in the ice-box at 40° C. for 7 months have a variable loss of titer. This loss is not sufficient to be of differential diagnostic value.

Heimoff,<sup>123</sup> on the basis of 8 cases, believes that tetanus toxoid stimulating doses ("booster shots") are apparently capable of causing biologic false positive reactions.

Loveman,<sup>188</sup> on the basis of 100 cases of false positive serologic reactions for syphilis, thought that the reactions were probably the result of both routine Army immunizations and upper respiratory infections, but that the former played the more important rôles.

A most significant study of this problem is that by Rein and Elsberg.<sup>248</sup> Because it summarizes the essential facts regarding the relationship between vaccinia and biologic false positive serologic reactions for syphilis, it is cited *in toto*.

**"Vaccinia.** A group of individuals who received routine smallpox vaccinations were examined 1 week later. Eighty had developed vaccinia and 49 had developed vaccinoid reactions. Blood specimens were obtained from these 129 individuals for serologic examination. This was repeated at weekly intervals. All serums were subjected to a battery of 6 serodiagnostic tests including the Kline Diagnostic, Kline Exclusion, Boerner-Jones-Lukens, Mazzini, Kahn and Kolmer procedures. There were 58 (44.9%) who developed doubtful and positive serologic reactions with 1 or more tests in this serodiagnostic battery. In this group of serologic reactors, 50 (86.2%) developed their first positive serologic reaction between the 8th and 14th day following the vaccination. Three (5.1%) developed the first positive serologic reactions on or before the 7th day and 5 (8.6%) developed the first positive serologic reaction between the 15th and 21st day following the vaccination.

"Of the 80 individuals with vaccinia reactions, 41 (52.2%) developed false positive blood tests, whereas of the 49 individuals with vaccinoid reactions, 17 (34.7%) developed false positive blood tests.

"This would seem to indicate that false positive tests will occur more frequently in individuals with vaccinia reactions, as compared to those with vaccinoid reactions. It should be pointed out, however, that the incidence and titer of the false positive serologic reactions was not entirely influenced by the type of severity of immunologic response to the vaccine virus. It was observed that many individuals with marked vaccinia reactions associated with axillary adenopathy remained serologically negative throughout this investigation, while other individuals with slight vaccinoid reactions developed high titered false positive serologic reactions. It would appear, therefore, that certain individuals ('serologic reactors') were more likely to develop positive serologic reactions than others, and the type of vaccination reactions was of only secondary importance. It is also true, however, that in a group of individuals who are 'serologic reactors,' the incidence and titer of the serologic reactions will be much higher in the vaccinia than in the vaccinoid group. Furthermore, there is some evidence to suggest that these serologic reactors will develop false positive blood tests as a result of other non-syphilitic conditions.

"Similar investigations were carried out in individuals who received 3 typhoid immunizations at weekly intervals and 3 tetanus immunizations at 3-week intervals. Although the series was too small to warrant any definite conclusions, it seemed that the incidence and titer of false positive serologic reactions was relatively insignificant."

*(The latter half of this article, with references, will be published under Dermatology and Syphilology in the October issue)*

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## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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## THE TONSIL-ADENOID PROBLEM

BY NOAH D. FABRICANT, M.D.

RELEGATED for some time to a scientific exile and characterized by a notable decrease in the number of articles published, there has been a recent breaking out afresh of interest in the subject of tonsils and adenoids. This recrudescence has been channelized in three major directions: the medico-surgical aspects, never comprehensively established; the relation of tonsillectomy to poliomyelitis; and the application of irradiation to hypertrophied lymphoid tissue in the nasopharynx as a means of treating certain types of impairment of hearing.

**Medico-surgical Aspects.** According to Reimann and Havens,<sup>17</sup> the causative relationship of infections about the teeth and tonsils to systemic disease is unproved and the removal of teeth and tonsils in an effort to influence the course of systemic disease is unjustified in the majority of

cases. Citing the criteria for the diagnosis of chronically diseased tonsils, they point out that local evidence of disease frequently disappears if recovery from the general disease ensues and that tonsils, particularly in malnourished, underweight or otherwise subnormal children, probably would become "normal" in appearance spontaneously if the general health were improved by hygienic measures. They believe, further, that large groups of persons whose tonsils are present are no worse off than those whose tonsils are out; that patients whose teeth or tonsils are removed often continue to suffer from the original disease for which they were removed; that beneficial effects can seldom be ascribed to surgical procedures alone; and that beneficial effects which occasionally occur after surgical measures are often outweighed by harmful effects or no effect at all.

"When should the tonsils be considered a menace to a child's development?" asks Kaiser.<sup>14</sup> In a study of 4400 children over a period of 10 years records were kept of the incidence of common infection of the upper respiratory tract, bronchitis, pneumonia and the various manifestations of rheumatic infection. Tonsillectomy was advised for all of the 4400 children, but only half of the group submitted to the operation; and none of the children in the control group of 2200 were operated on during the succeeding years. Kaiser found that markedly hypertrophied tonsils and tonsils that are repeatedly inflamed, giving rise to attacks of tonsillitis and cervical adenitis, often impair normal physical development and that such infections as the common cold, otitis media, sinusitis and laryngitis may unfavorably influence the child's normal development. But he was unable to demonstrate that tonsils frequently are a causative factor in these infections. Removal of tonsils does not seem to reduce the incidence of bronchitis, pneumonia or tuberculosis. By reducing the number of infections of the throat, tonsillectomy appears to benefit the rheumatic child. He concludes that in approximately 20% of children the tonsils are either hypertrophied or diseased sufficiently to have an unfavorable influence on the development of the child and that such tonsils should be removed.

Paton<sup>16</sup> carefully studied a series of 909 school girls over a period of 10 years, the decade of the 1930's. Of this group, 516 had their tonsils removed and 393 had not. By comparing the two groups and employing the non-operated group as a control approximating normal, he attempted to provide data which would indicate the effect of operation as related to future health. He found that the group operated upon was no healthier than the control group on arrival at school; while at school, the group operated upon was less healthy than the control group, as shown by the number of school days lost through illness. The group operated upon suffered less from tonsillitis but was more subject to respiratory infections, and lost more days from bronchitis alone than they gained in respect to tonsillitis. When the small groups on whom a single operation was performed (tonsil operation, 57 cases; adenoid operation, 24 cases) were considered, two deductions were arrived at. First, removal of tonsils is the factor in the combined operation responsible for the reduction in tonsillitis and for the increase in respiratory infections; second, removal of adenoids appears to be followed by certain definite effects. Adenoidectomy alone reduces the liability to respiratory infections, but in the combined operation group, the removal of adenoids failed to counteract the increase in respiratory infections which resulted from the tonsillectomy. Removal of adenoids increased the liability to acute otorrhea, while recurrent attacks were seldom prevented. In general, many of these findings appear to

support the contention made in England more than a decade ago that a large proportion of the tonsil and adenoid operations now done in children are "unnecessary, entail some risk, and give little or no return."

In the management of frequent colds, sinusitis, bronchitis and recurrent pneumonia Hansel and Chang<sup>12</sup> stress the possibility of allergy as an etiologic factor. Of 200 children considered as a routine for removal of the tonsils and adenoids because of these complaints, a diagnosis of nasal allergy was established in 13%. Removal of tonsils and adenoids in allergic children should not be performed during hay fever seasons, and the indications for operation should be the same as in non-allergic children. Tonsils and adenoids should not be removed with the idea of alleviating allergic symptoms.

Data on school attendance and gain in weight for tonsillectomized and for non-tonsillectomized children were obtained by Ashley<sup>1</sup> who made a study on 1524 school children in a community under average normal conditions of American life. Of the total number, 602 children had previously had their tonsils removed and 922 had not. The tonsillectomized group lost slightly less time from school than did the group of non-tonsillectomized children, but the difference was so slight as to be insignificant. After tabulating the gains in weight, it was found that the total gain was greater for the tonsillectomized group, and that the total gain in weight for the first year in school for the tonsillectomized group was almost twice that for the non-tonsillectomized group.

The indications for tonsillectomy are considered under three classes by Coates and Gordon,<sup>4</sup> namely: conditions within the tonsils; conditions remote from the tonsils; and conditions adjacent to the tonsils. They state that conditions within the tonsils indicating tonsillectomy are: repeated attacks of tonsillitis; abscess within the tonsils; epidemic streptococcic sore throat; tuberculous tonsils; diphtheritic tonsils; hypertrophied tonsils; Vincent's infection of the tonsils; and halitosis due to infection of the tonsils. Conditions adjacent to the tonsils indicating tonsillectomy are: acute catarrhal and suppurative otitis media; chronic suppurative otitis media; middle-ear deafness; labyrinthitis and inner ear deafness; sinusitis; thyroid disease; laryngitis; pharyngitis; cervical adenitis; peritonsillar abscess; acute phlebitis of cervical veins; and ocular diseases. In a discussion of conditions remote from the tonsils that indicate tonsillectomy, a lengthy list of acute and chronic processes traceable to a primary focus of infection is cited. It is maintained that in the management of such infections the closest coöperation of the internist, pediatrician, general practitioner and the otolaryngologist is advisable. The authors scorn injudicious tonsillectomies. Shambaugh<sup>20</sup> believes that tonsils and adenoids should be removed when there is evidence that they are the seat of chronic infection which is producing, or threatens to produce, bodily injury greater than the dangers, disability, discomfort and inconvenience of removal. Emenheiser<sup>7</sup> does not believe that the consistency of the tonsil or the presence of a yellowish secretion in the crypts is a reliable guide in making a diagnosis of infected tonsil. The preservation of the human race or the survival of the fittest, he concludes, does not depend on tonsillectomies.

**Relation of Tonsillectomy to Poliomyelitis.** Several clinical reports of bulbar poliomyelitis following the removal of tonsils and adenoids prompted Sabin<sup>18</sup> to investigate experimentally its relationship. He found that while mere transitory contact of the virus with the normal or injured pharynx or tonsils of monkeys will not produce poliomyelitis, it is possible

to infect these animals when the virus in quantities of from 100 to 1000 minimal cerebral infective doses is injected into the tonsillopharyngeal region. The high incidence of the bulbar type of the disease among monkeys and evidence that the virus did not invade the central nervous system along the olfactory pathway indicated to him that after tonsillopharyngeal injection the virus progresses along a local peripheral nerve. It is concluded that the season of high incidence of poliomyelitis is an unfavorable period for operations in the upper air passages.

Observations on an occurrence of 5 cases of the bulbar type of poliomyelitis in a family of 6 children following general tonsillectomy were reported by Francis and his associates Krill, Toomey and Mack.<sup>9</sup> The youngest child, but  $2\frac{1}{2}$  years of age, was not operated on and did not contract the disease. In an effort to determine the sources of the infection, extensive epidemiologic studies were undertaken and the activities of the family were reviewed in detail chronologically. Virus studies were made on the stools of 54 persons, and particular emphasis was placed on the children's associates. Virus was found in the stools of the youngest, unoperated child, in the stools of 6 cousins whom the children had visited and with whom they had been in intimate contact prior to their operations, and in the stools of 3 children of a family who were close playmates. The authors are convinced that tonsillectomy performed on an infected subject is the provocative factor in precipitating the bulbar type of poliomyelitis in a person who otherwise would probably escape with inapparent infection.

After reviewing the available literature and undertaking an analysis of statistics obtained from public health authorities, hospitals and a survey of a severe epidemic of poliomyelitis in Wichita, Kan., in 1940, Seydell<sup>10</sup> thinks it probably safe to say that tonsillectomy has no bearing on the incidence of spinal meningitis. A comparison of the statistical data in the literature showed that in all instances the percentage of tonsillectomized patients with the bulbar type is far greater than that of tonsillectomized patients with the spinal type. He holds that it will be necessary to institute other complete epidemiologic studies before this question can be answered, namely: Is the average person who has had a tonsillectomy more susceptible to poliomyelitis of the bulbar type than one who has not had this operation?

Like Seydell, Aycock<sup>2</sup> collected a vast amount of data on the relation of tonsillectomy to poliomyelitis from various hospitals, city and state health departments, numerous personal communications and 52 articles in the literature. Aycock writes that the results of his study are in keeping with other epidemiologic indications that some added circumstance determines the form of the disease which develops upon exposure to the virus of poliomyelitis and that this circumstance resides not so much in parasitic factors or in environmental conditions affecting exposure as in factors of autarcesis (the natural ability of the body to resist infection) in the host. There is a casual relationship between the removal of tonsils and the onset of bulbar poliomyelitis within the time interval corresponding to the incubation period of the disease. The statistics collected do not lend themselves to analysis whether or not the absence of tonsils predisposes to clinical poliomyelitis, with one exception. In this instance, cases of poliomyelitis gave a history of removal of tonsils with greater frequency than controls in the same area. It is shown, however, that the relative frequency of the occurrence of the bulbar, as compared with the spinal, form of poliomyelitis is greater at all ages in persons giving a history of previous tonsillectomy. Because of the numerical considera-



tions, the hazard of bulbar rather than spinal poliomyelitis in tonsillectomized individuals hardly constitutes in itself a contraindication to the operation. Although the risk should be recognized, the decision for the operation should rather be based upon the indications in the individual case. The selectivity seen in the occurrence of bulbar poliomyelitis following tonsillectomy and its relatively more frequent occurrence in tonsillectomized individuals comprise a demonstration that the nasopharyngeal mucosa may be the locus of at least one added circumstance which determines the outcome of exposure to the virus, and is important not only as indicative of the *modus operandi* of autarcesis, but as providing a means of prevention. Since this operation is practically always elective as to time, changing the season when it is done, so as not to coincide with the season of poliomyelitis prevalence, would eliminate numbers of cases of the highly fatal bulbar form of the disease.

In order that additional information on tonsillectomy and poliomyelitis might be gained, Page<sup>15</sup> consulted the records of Manhattan Eye, Ear and Throat Hospital and the Department of Health of the City of New York. As 1937, 1939 and 1941 were the years in which poliomyelitis was most prevalent, the patients who had tonsillectomies performed on them during these years were communicated with by mail; 27,849 cards were sent out by the Manhattan Eye, Ear and Throat Hospital, requesting that answers to the questions be written on a return postal card. On the return card were the patient's name, his age, his hospital number, the data of the tonsillectomy and the following questions: Have you had any illness since the tonsillectomy? What were the nature and the dates of illnesses, if any? A total of 8915 replies were obtained, and among them 1 instance of poliomyelitis was reported. For the same year (1937) in which 243 cases of poliomyelitis with 21 deaths were recorded by the New York Department of Health, 10,597 cards were sent out and 2545 replies were received. Similarly, in 1939 and 1941, cards were sent out. The data in the 7 replies that reported illnesses after tonsillectomies included spinal meningitis, tuberculous meningitis, and "infantile paralysis."

**Radiation in Impaired Hearing.** According to Crowe and Baylor,<sup>5</sup> a long-continued partial obstruction of the Eustachian tubes in children causes retraction of the tympanic membranes, impaired hearing for high tones with relatively good hearing for low tones and sometimes a total loss of hearing by bone conduction. In all the pharyngeal orifices of the Eustachian tubes of a group of 60 children nodules of lymphoid tissue caused partial occlusion. The location of the hyperplastic lymphoid tissue interfered with normal function of the tubes. The most satisfactory method of treatment they found to be irradiation with radium or Roentgen rays. After the hyperplastic tissue has been reduced and the tubal orifices appear normal, the hearing for high tones and for bone-conducted sounds often returns to normal, and it remains there as long as the Eustachian tubes are clear. After a cold, however, the original condition may recur, with consequent loss of hearing. If the causal condition is recognized and treated before the age of 15, hearing usually returns to somewhere near the normal level. After this age the results are far less satisfactory, because hyperplastic lymphoid tissue and partial tubal obstruction usually date from early childhood. After the age of 15, the secondary changes in the middle ear may be so advanced that they can be repaired by no treatment whatever. Irradiation does not permanently remove hyperplastic lymphoid tissue, but relatively small doses keep it in abeyance

during the age period in which it grows most actively. Crowe<sup>6</sup> finds that lymphoid tissue is so sensitive to radiation that the dosage employed in treatment is far below the amount that cause injury to the mucous membrane or surrounding structures. If used carelessly, radium therapy may be extremely dangerous. It should never be given in the presence of acute nasopharyngitis. Radiation is of no value in the treatment of chronic middle-ear suppuration, otosclerosis or any form of inner ear or nerve deafness. It is used for the sole purpose of reducing obstructing nodules of lymphoid tissue, decreasing the secretion of mucus and restoring the normal ventilating function of the Eustachian tube. For this reason radiation is more often beneficial in children than in adults.

A statistical study by Guild<sup>11</sup> and his associates of the hearing of 1365 Baltimore school children selected at random, between 8 and 14 years of age, revealed that impaired hearing for high tones is by far the commonest form of auditory defect in children, and occurs more often in boys than in girls, more often in winter than in autumn, and more often in older children. Of these children, 41.2% had some form of impaired hearing, but only 2.9% had a loss for conversational voice. More than half of the children had previously had their tonsils removed, but incidence of impaired hearing was almost the same in the 2 subgroups. No relationship existed between the incidence of hearing defects and condition of the teeth, height or weight for the age, or any of several other measurements made. The authors declare that irrespective of whether or not radon therapy, surgery or some other method of treatment proves best, the problem of the prevention of impaired hearing in children is of such magnitude that the coöperation of otologists, public health agencies, school authorities and family physicians will be needed for its successful practical solution.

Fricke and Brown<sup>10</sup> treated 82 patients with hypertrophied lymphoid tissue in the nasopharynx with radium, and of these 76 could be traced: 61 patients complained chiefly of deafness and tinnitus; in 15 the main complaints were frequent colds and severe sore throats. Hypertrophied lymphoid tissue, especially in the nasopharynx and the fossa of Rosenmüller, was present in all. Gamma rays of radium were employed. A straight metal rod ending in a brass tube containing radon was used. Definite and permanent improvement was obtained in 45 of the 76 patients, temporary improvement in 13 and no improvement in 18. The younger patients showed the best response to therapy.

Burnam<sup>3</sup> describes his technique in reducing the lymphoid tissue in the nasopharynx of children for improvement of hearing, but since his report Emerson<sup>8</sup> and his associates have designed simple appropriate instruments and established a technique they claim is within the reach of most clinics. It allows efficient irradiation of the lymphoid tissue at the orifice of the Eustachian tube with 25 mg. radium. Each needle is 20.3 mm. long, with an external diameter of 1.35 mm. Jones<sup>13</sup> describes and illustrates a radon applicator designed for office use which contains 100 millicuries of radon and finds its use for office treatment has proved satisfactory.

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## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 20, 1945

#### Enzymological Investigations on Experimental Tuberculosis in Rabbits.

CHARLES WEISS and NELLIE HALLIDAY (Laboratories, Jewish Hospital, Philadelphia). Several investigators, including Moen, have come to the conclusion that the specific toxic action of tuberculin upon hypersensitive tissues is probably not the result of an antigen antibody reaction. The discovery, by the present authors, of a selective inhibitory action of tuberculo-carbohydrate and tuberculo-phosphatid upon endocellular enzymes (Cathepsin II) derived from tissues of animals infected with tubercle bacilli throws new light upon this mechanism and suggests an enzymologic explanation, as follows: Since cathepsin is the enzyme which is concerned with the processes of cellular growth and repair, inhibition thereof leads to injury of the cells. Tuberculin is more toxic for tuberculous than for normal cells in tissue culture because two of its important constituents (phosphatid and carbohydrate) exert a selective inhibitory action upon the proteinases of the former.

Our observations may also throw light on the mechanism of caseation and softening. As pointed out by Jobling and Petersen, "caseation in tuberculosis is a form of coagulation necrosis in which the dead tissues rarely undergo autolysis, except as a result of secondary infection." It is quite likely that inhibition of autolysis is accomplished by the carbohydrate and phosphatid fractions of the tubercle bacilli.

#### Anticonvulsant Effects of Steroids. H. T. WYCIŚ and E. A. SPIEGEL

(Department of Experimental Neurology, Temple Univ. Medical School). Continuing former studies (E. Spiegel, *Proc. Fed. Am. Soc. Exp. Biol.*, 2 (1), 1943) anticonvulsant effects were observed on white female rats with androstenedione, dehydroandrosterone, desoxycorticosterone acetate, acetoxyprogesterone, progesterone and testosterone. The following substances had no or only a questionable anticonvulsant action: cholesterol, allocholesterol, cholesteryl bromide, epicholesterol, stigmasterol, stigmasteryl acetate,  $\alpha$ -spinasteryl acetate, ergosterol, ergosteryl acetate,  $\alpha$ -ergosterenyl acetate, dehydrocholic acid, desoxycholic acid,  $\Delta^5$ -3-acetoxy cholenic acid, sarsapogenin acetate, pseudosarsapogenin acetate, diosgenin acetate, pseudodiosgenin acetate,  $\alpha$ -estradiol benzoate (progynon B), theelin in oil, 6( $\alpha$ )acetoxy-progesterone (amorphous modification), etio-cholan-3 $\beta$ -ol-17-one acetate, 5-pregnen-3 $\beta$ -ol-20-one acetate, 5,16-pregnadien-3 $\beta$ -

ol-20-one acetate, stilbesterol. The anticonvulsant dose lies rather close to or is identical with the hypnotic dose for testosterone, progesterone and desoxycorticosterone; a definite margin between these doses exists for adrostenedione, dehydroandrosterone and acetoxypregnenolone.

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**A Method for the Uniform Production of Experimental Gastric Ulcer in the Rat.** HARRY SHAY, S. A. KOMAROV, M. GRUENSTEIN, H. SIPLET, and DAVID MERANZE (Medical Research Laboratory, Samuel S. Fels Fund, Philadelphia). After ligating the pylorus in properly fasted rats and allowing the gastric secretion to accumulate in the stomach, gastric ulceration will develop uniformly in the rumen, less often in the antrum, and least frequently in the body of the stomach. Ulceration results from the action of the accumulated unbuffered gastric juice in the stomach. The evidence for this is in the fact that ulcerations identical with those produced after pyloric ligation result in 3 to 4 hours after the gastric instillation in pylorus-ligated atropinized rats of: (a) human gastric juice; (b) rat's gastric juice; (c) an artificial acid-pepsin mixture similar in acidity and pepsin concentration to the natural gastric juice employed in the first two. Proper atropinization in the rat will inhibit gastric secretion for many hours. Furthermore, the lesions produced are clearly acid-pepsin ulcers because either neutralization of the acid or inactivation of the pepsin will prevent their formation. Because of these findings, we believe that this experimental method could be adopted readily for use as a rapid assay method for hormonal anti-acid or anti-ulcer agents. We have already utilized it for the study of acid neutralizing and anti-peptic agents *in vivo*.

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**A Study of the Intermediates of Acetate and Acetoacetate Oxidation With  $C^{13}$ .** J. M. BUCHANAN, W. SAKAMI, S. GURIN and D. WRIGHT WILSON (Dept. of Physiological Chemistry, Univ. of Pennsylvania). It has been known for years that acetoacetic acid is a product of fat metabolism and it has been thought that fat metabolism is distinct from carbohydrate metabolism. However, Breusch and Wieland and Rosenthal have recently advanced the hypothesis that acetoacetic acid is metabolized by way of the citric acid (or tricarboxylic acid) cycle which is recognized as a metabolic pathway for the oxidation of carbohydrates. We have been able to study this hypothesis directly by using the heavy isotope of carbon to mark the carboxyl and beta carbon atoms in acetoacetic acid so that they could be followed as the compound was changed by enzymes in a tissue.

Isotopic acetoacetic acid was incubated with an homogenate of guinea-pig kidney. Using a suitable experimental procedure, we found isotopic carbon of acetoacetic acid in  $\alpha$ -ketoglutaric and fumaric acids, compounds commonly recognized as intermediates in carbohydrate oxidation. Most of the isotope in  $\alpha$ -ketoglutaric acid was in the carboxyl distal to the keto group. This indicates that cisaconitic acid may be an intermediate in acetoacetic acid oxidation but that citric acid is not. On account of the possibility that  $CO_2$  might be formed from isotopic acetoacetate and might react to form isotopic fumaric acid, a control experiment was run which showed that such was not the case in our experiments.

As we have shown that acetoacetate may be metabolized by way of the tricarboxylic acid cycle, it was thought probable that acetate might be metabolized in the same way. Sodium acetate with excess  $C^{13}$  in the

carboxyl group was incubated with an homogenate of guinea-pig kidney and isotope was later found in succinic acid, an intermediate between  $\alpha$ -ketoglutaric and fumaric acids. These findings indicate that acetate and acetoacetate are probably metabolized by the same pathway.

**Subdivision of the Lung on the Basis of Bronchial Distribution.** JOHN FRANKLIN HUBER (Dept. of Anatomy, Temple Univ. Medical School). From the smallest branches of the dividing bronchi, the irregular, thin-walled expansions form the air spaces from which gaseous exchange between the blood and air takes place. The total branching of each the right and the left bronchus (together with supporting tissue, blood-vessels, nerves and lymphatics) is a lung. It follows from this, that the ultimate or total branching of any bronchial branch, no matter what size, is a portion of the lung to which the name "bronchopulmonary segment" can be logically applied.

The largest bronchial branches form segments of the lung which are usually separated (at least in part) from each other by fissures and have, therefore, long been accepted as definite entities called lobes. On the right there are two fissures—three lobes, and on the left, one fissure—two lobes.

The next order, bronchial branches, also form segments which are definite entities in spite of the fact that they are usually not separated by fissures. These segments can be proved to be entities by several procedures, including injection of a colored gelatin mass into the segment, inflation of the segment and dissecting the segments free from each other. Added proof comes from the fact that extra fissures are seen which do separate these segments.

The author has suggested elsewhere (with Dr. Chevalier L. Jackson) that not only should the main bronchial branches be named according to their lung segment, such as "right upper lobe bronchus," but the next order branches be designated by the subdivisions of the lobes which they form, for example, "bronchus to the ventral segment of the right upper lobe."

# BOOK REVIEWS AND NOTICES

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ORGANIC CHEMISTRY. By LOUIS F. FIESER and MARY FIESER. Pp. 1112; numerous figs. Boston: D. C. Heath, 1944. Price, \$8.00 (trade edition); \$6.00 (college edition).

THIS is an excellent and modern work on organic chemistry which should prove to be of great interest to the biochemist as well as the organic chemist. The first portion of the book is devoted to a moderately elementary development of the subject and includes a good discussion of aliphatic and alicyclic chemistry. The latter half of the volume is a superb presentation of aromatic chemistry.

Interspersed throughout the book are essay chapters on special topics which will add immeasurably to the value of this text. These topics include Petroleum, Rubber, Fats and Waxes, Proteins, Microbiological Processes, Rôle of Carbohydrates in Biological Processes, Metabolism of Fats, Metabolism of Proteins and Amino Acids, and Dyestuffs. To those who are well acquainted with these fields, there will perhaps appear to be errors of omission which are obviously due to limitations of size and scope imposed upon the authors. Those who are unfamiliar with these fields will find that the Fiesers have summarized them in excellent fashion.

The publishers have done an excellent job; the binding, type, and paper are very satisfactory. There are remarkably few errors to be found. Mention should likewise be made that the book is very carefully indexed. In the Reviewer's opinion the Fiesers have made an outstanding contribution to the field.

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S. G.

ARTHRITIS AND ALLIED CONDITIONS. By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Associate in Medicine, Univ. of Penna.; Senior Ward Physician and Chief of the Arthritis Clinic, Hospital of the Univ. of Penna. Third Ed., enlarged and thoroughly revised. Pp. 1359; 329 ills. Philadelphia: Lea & Febiger, 1944. Price, \$12.00.

THE ability of such a large book as this to reach 3 editions in 5 years loudly announces that it meets a need and suggests strongly that it meets it well. "Because of the generous assistance of numerous colleagues and friends, it has been possible to include in this 3rd edition 13 additional chapters and more than 100 new photographs. Extensive changes have been made in the text so that the subject matter is brought up to the minute; practically every page has been revised or rewritten in an effort to exclude antedated material and to include all newer important developments. New chapters have been added on such subjects as penicillin, psychogenic factors in rheumatic diseases, rheumatic manifestations of tropical diseases, recent advances in arthritis and allied conditions, common mistakes in arthritis and allied conditions, Dupuytren's contracture, diagnostic digest of the average arthritic problem for the general practitioner, effect of climate upon arthritis, occupational therapy, and differential diagnosis of rheumatoid arthritis for the practitioner." Also the chapter on massage has been enlarged and enriched with photographs. A new introductory chapter presents a diagnostic digest of the average arthritic problem for the general practitioner and another chapter on treatment from the same point of view. The text has been expanded by about 15% without increasing the size of the volume, by using a larger, though not unpleasant, page plate size. Treatment is emphasized throughout; the Reviewer, not a practicing physician, is not qualified to pass on such matters.

Some critics might take exception to some statements, especially in the

chapter on sciatica, and query the relevancy of some of the presentations in a book on Arthritis—but in any case these are infrequent and often minor points. The “boxing” of chief items in this work, a novel and useful practice in medical books, has been continued from previous editions.

The illustrations, especially the frequent Roentgen rays, are excellent. In fact, the whole production, though complying strictly with wartime restrictions, seems more like the pleasanter and more satisfactory products of peacetime publishing.

One might well wonder how a busy physician could accomplish the work required by these 3 editions; but only if one did not know the Author.

E. K.

**MEDICAL CLINICS OF NORTH AMERICA.** Philadelphia Number. Symposium on Recent Advances in Medicine. November 1944. Pp. 1293 to 1608. Index for 1942–1944. Philadelphia and London: W. B. Saunders, 1944. Price, \$16.00 per yr.

THIS number of the Medical Clinics is written by doctors from Philadelphia, and the material is presented in 2 parts. The first half of the volume consists of a symposium that includes Cardiovascular Diseases, Otolaryngology and the Leukemias. Miller and Breitwieser have written a valuable survey for the field of Gastro-enterology, and Kern discusses the management of Rabies. Also covered are the use of Thiouracil and the epidemiology of acute respiratory tract infections, while Mudd presents a study of air conduction of disease.

The second portion of the volume is made up of work done by the Pennsylvania Hospital Unit on diseases of the tropics. The articles include the diagnosis and management of the Dengue Fevers, Leprosy, Scrub Typhus, Malaria, and the Dysenteries. Functional problems are discussed by Rush and Vander Veer who studied the Anxiety Neuroses as manifested in Gastro-intestinal and Cardiovascular Symptoms.

M. H.

**SOLDIER TO CIVILIAN.** Problems of Readjustment. By GEORGE K. PRATT, M.D., Psychiatric Examiner, U. S. Armed Forces, Induction Center, New Haven, Conn.; Formerly Assistant Clinical Professor of Psychiatry, Yale University. Foreword by GEORGE S. STEVENSON, M.D., Medical Director, The National Committee for Mental Hygiene. Pp. 231. New York: McGraw-Hill Book Co., 1944. Price, \$2.50.

THIS book is addressed “primarily to the families, and prospective employees of all returned service men.” The treatise is discussed in the following chapters: Introduction. What Equipment Did the New Soldier Take with Him? What Did Military Service Do to the Former Civilian? How the Army Prevents Strains of Adjustment. Soldiers with Psychiatric Disabilities. The First Weeks at Home. Going Back to Work. Getting Reacquainted with the Family.

Emphasis is placed on the returning soldier who is physically or mentally handicapped. It is inferred that in the latter group are those who, through intellectual or emotional impairment, have become less efficient or less happy than they were previously. With no claim that his classification is scientific, the writer offers several groups. *The insanities or psychoses* affect subjects most of whom will require detention in mental hospitals. *The mentally defective* is one who has been endowed with less than the normal mental equipment, therefore, he must not be expected to assume the responsibilities of more fortunate individuals. *The psychopathic personalities* are different from the preceding group—they show character distortion; being unable to profit by experience, such individuals are apt to continue to be a grave problem to their families and to Society. *Structural diseases of the nervous system*: here may be shown either physical or mental impairment, for instance, as by fracture of the skull, or by syphilis of the central nervous system. Some such subjects may be treated and cared for at home. *The combat fatigue*

*disorders*: these constituted the emotional group of World War I, then erroneously classed as "shell shock" patients, since but few had been exposed to shell fire. Under present-day methods, many are returned to full duty or to less demanding work. *The psychoneurotic*: this, by far the largest group, consists of those who show various anxiety states, psychosomatic disorders, obsessive or compulsive manifestations, or who are beset by fears and phobias. Of this group, it is believed that about 80% have had a latent predisposition to the disorder. A few may have been genuine malingerers and many have been discharged from the service for "psychopathic disability."

An Appendix discusses Community Services for Veterans. The suggestions and advice offered in this volume are excellent. N. Y.

OURSELVES UNBORN. An Embryologist's Essay on Man. The Terry Lectures. By GEORGE W. CORNER, Director of Department of Embryology of the Carnegie Institution of Washington and Professor of Embryology in Johns Hopkins Medical School. Pp. 188; 18 figs. Connecticut: Yale Univ. Press, 1944. Price, \$3.00.

THE Author, an anatomist of high repute, here expounds the story of the development of the human embryo in its first few weeks of life ["When a man is born he is already 9 months old"], using photographs, beautifully designed diagrams, and reference material from other animals to portray the full picture in lucid form. "To the seeing eye the human embryo from egg to birth is an archive in which is written the evidence of its descent as an animal, a vertebrate, an amniote, a mammal, a primate; and it is an organic germ in which the gift of life is intrinsically bound up with the necessity of growth and of ineluctable change."

Included is an excellent presentation of the pathogenesis of embryonic disease, classified under (a) Defects of Fertilization, (b) Defects of the Maternal Environment, and (c) Defects of the Egg, the Sperm Cell and the Embryo. Here are discussed such timely matters as disturbances in tissue organizers, the tragic sequels of maternal German measles during the first months of pregnancy, and the genetic background of erythroblastic fetalis. It is a surprise to learn that in most mammals 20 to 50% of all conceptions succumb before birth, and that for humans the prenatal mortality is estimated as 1 out of every 3 pregnancies. "Those of us who survive are truly the elect, chosen from a larger multitude." A review of comparative anatomy and embryology shows that man differs from his close relatives the apes and monkeys in having a more general, less highly specialized anatomic structure, capable of widely diversified activities under the guidance of his superior free-functioning brain.

Dr. Corner has the imagination and wisdom to see the cultural relationships between the intricacies of his own highly specialized subject and the basic human problems which perplex all thoughtful minds. Modern embryology can offer pertinent significances to such intensely personal yet universal problems as the origin of individual man, the fore-ordaining of one's characteristic traits, and the relationship of our human bodies and souls to all other kinds of living creatures. He writes with grace and humor, and has a fine mastery of English style, which is an accomplishment possessed by but few leaders in American science. Never dull or confusing, his descriptions of the intricacies of embryonic and placental development are indeed easy to follow. This essay is thus more than a philosophically tinged exposition of a learned specialty; it can be deemed a proud contribution of modern biology to contemporary world literature.

I. W.

HANDBOOK OF INDUSTRIAL PSYCHOLOGY. By DR. MAY SMITH. Pp. 304. New York: Philosophical Library, 1944. Price, \$5.00.

It is not this Author's purpose to furnish a detailed chronicle of industrial psychology, but one "to provide an introduction to the subject for those who are in some way responsible for others, or who have to get on with others."



Dr. Smith describes her branch of science as "the study of the conduct of those who exchange the work of their hands and brains for the means to live." The chapters are: Pioneer Work; Fatigue in Industry; The Environment; Finding the Job for the Person and the Person for the Job; Time and Motion Study; Temperaments, Particularly the Nervous; Why We Work; Measure of Human Well-being; General Hints on Methods of Investigation; Conclusions.

As to the chapter on "Temperaments," one finds nothing of greater merit in medical literature. This portion of her discourse is discussed as: history and classification; the nervous person; expression of nervousness in (a) work, (b) sickness, relations to people, (c) must the nervous person break down? Heretofore, the Author's work has been of signal service to the Board of Medical Research Council's Industrial Health Research. This contribution will be of especial significance to those who view with gravity the approaching post-war period.

N. Y.

AMERICAN MEDICAL PRACTICE IN THE PERSPECTIVES OF A CENTURY. By BERNHARD J. STERN, PH.D., Lecturer in Sociology, Columbia University; Visiting Professor of Sociology, Yale University. Pp. 156. New York: The Commonwealth Fund, 1945. Price, \$1.50.

THIS monograph presents the social aspects of medical practice as they have evolved during the past century, and in the first 2 chapters the relationship of the fundamental social changes in American life and the development of medical practice is discussed.

The changing pattern of medical practice is described in the next 4 chapters, dealing with the relation of the specialist and the general practitioner, the supply and distribution of physicians, the patient load carried by various types of medical practitioners, and the income of physicians. The facts revealed by a number of recent studies of medical practice are reviewed and discussed, particularly as indicating the need of revision in the present-day methods of medical service.

The final chapter on the distribution of medical services directs attention to the consumer of these services, and to his difficulties in financing present standards of medical care in communities where such care is obtainable. It is pointed out that the quantity and quality of medical care obtained by the consumer is largely determined by his economic status, and that although the lower economic groups have the greatest need for medical service, they get the least care. The medical care of Negroes is discussed at some length as an example of this paradoxical situation.

Unmet medical needs in this country are disturbing the American people and are stimulating legislative action as a means of solving these problems.

This monograph is the first of a series planned by "The Committee on Medicine and the Changing Order" of the New York Academy of Medicine, which hopes to provide a framework for an understanding of the current medical situation and its trends. The purpose of the Committee is admirably carried out in this first monograph; and if the same standard of excellence is maintained in those to follow, the series should be of much value both to the medical profession and to the general public in gaining a better understanding of the confused problems of medical service in our present-day complex Society.

G. R.

THE TRIALS AND TRIUMPHS OF THE SURGEON, and Other Literary Gems. By J. CHALMERS DA COSTA, M.D., LL.D. Edited by FREDERICK E. KELLER, M.D. Pp. 401; no ill. Philadelphia: Dorrance, 1944. Price, \$5.00.

THOSE who recall the eagerness with which much of medical Philadelphia flocked to hear the Author of these essays will be glad for this opportunity to refresh their memories. Those who never heard da Costa's speeches, full of brilliant allusions and trenchant, even biting, sarcasm about medical evils, could do worse than to become acquainted with these virile lively essays.

When attracted by such subjects as the unjustifiable longevity of objectionable people, or amused by "a man so stupid that he got splinters in his fingers if he scratched his head," and similar Bob Hope-isms, we should not neglect the deep truths that they sugar-coat. The newcomer must not be surprised at a style admittedly florid even a generation ago; idiots always gibber, fear produces its cold tremor, well-worn Gilbert and Sullivans do their turns, Tennyson's argosies of the skies and, especially *a propos* at this time, his Federation of the World, fulfill expectations by their presence. We miss the celebrated Blockley address, describing its ancient evils such as the "Board of Buzzards," whose members were "like corkscrews, the crookeder they were, the more pull they had!" One regrets the lack of any dating of the various items, for this book has durable worth; but this is a small matter compared to the positive values that Dr. Keller gives us in this interesting collection of essays.

E. K.

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**SHOULDER LESIONS.** By H. F. MOSELEY, M.A., D.M., M.Ch. (Oxon.), F.R.C.S. (Eng. and C.), F.A.C.S., Montreal, Canada; Lecturer in Surgery, McGill University; Assistant Surgeon, Royal Victoria Hospital. Pp. 181; 70 figs. Springfield, Ill.: Charles C Thomas, 1945.

THE value of a monograph on "Shoulder Lesions" is readily appreciated by every one who meets the problems created by these lesions clinically. Shoulder pain is a frequent presenting symptom and often proves to be very baffling to the diagnostician and rather resistant to empirical treatment. Dr. Moseley's monograph is written simply and clearly. It reveals an extensive personal experience and a large amount of original observation. Chapter V on the "Calcified Deposits in the Rotator Cuff" will be of particular interest not only to specialists in this field but to medical practitioners in general and to medical students and house officers.

The chapter on the "Neurological Aspects of Shoulder Pain" and on Roentgen ray diagnosis and treatment have been contributed by colleagues who are specialists in these fields. The book should be of great value to the physician who wants a ready reference for helpful suggestions in the diagnosis and management of shoulder lesions.

J. R.

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**INTERNAL MEDICINE.** Its Theory and Practice. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine, Tulane Univ. of Louisiana School of Medicine; Senior Visiting Physician, Charity Hosp., New Orleans, La. CONTRIBUTORS: Fuller Albright, Edgar Van N. Allen, David P. Barr, Harvey Bartle, Jr., Arthur L. Bloomfield, Leslie A. Chambers, Alan M. Chesney, Robert A. Cooke, Charles F. Craig, Ernest C. Faust, Grace A. Goldsmith, Frederic M. Hanes, William J. Kerr, Ralph A. Kinsella, Edward B. Krumbhaar, William S. McCann, James H. Means, Stacy R. Mettier, James A. Miller, Francis D. Murphy, John H. Musser, O. H. Perry Pepper, Maurice C. Pincoffs, Hobart A. Reimann, Charles Rupp, Fred M. Smith, Wesley W. Spink, Randall G. Sprague, Frank E. Stevenson, Edward A. Strecker, Cyrus C. Sturgis, Russell M. Wilder, George Wilson. Fourth Ed. Pp. 1518; 66 ills. Philadelphia: Lea & Febiger, 1945. Price, \$10.00.

THIS standard work was originally written with two distinct objectives in mind. It was designed to give to the undergraduate student a textbook written by a limited number of well-qualified authors who would be able to present the essentials without allowing the work to become encyclopedic in size and impractical for study or handling. Its second purpose was to give to the practitioner of medicine a work of ready reference so documented that he could go at once to the sources of material or to the outstanding contributions of medical literature for more detailed information. In this 4th edition these purposes have been well fulfilled.

The new material which has been added to this work has required nearly 100 more pages than the previous edition, in spite of the deletions made in

many sections. These numerous changes and additions deal for the most part with the newer therapies; the sulfonamides, penicillin, thiouracil and many others. A certain amount of space has been devoted to the problems of war medicine, notably in conjunction with the protozoan and metazoan diseases and the acute infectious diseases. Military neuropsychiatric disabilities, war neurology and altitude sickness all receive due attention.

Nineteen of the 26 chapters are prepared by heads of medical school departments, the remaining 7 by authors who are heads of special divisions in departments of medicine. All of them are teachers of wide experience and authorities on the subject with which they deal. They know what to say and how best to say it and they are experienced writers as well as teachers. The subject matter is restricted to the practical rather than the theoretical. The material is well organized and its authorship vouches for its authority.

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CONTAGIOUS DISEASES. A Guide for Parents. By W. W. BAUER, B.S., M.D., Director of Bureau of Health, Amer. Med. Assn.; Assoc. Editor of *Hygeia*; formerly Epidemiologist, Milwaukee Health Dept.; Lecturer in Public Health, Marquette Univ. Pp. 188; no ills. New York: Knopf, 1944. Price, \$2.00.

THIS new edition is a worthwhile text which will make a place for itself in the health libraries of intelligent parents throughout the United States. After a fairly technical introduction, Dr. Bauer discusses quarantine and the Health Department, home nursing, and the more usual contagious diseases. He writes with common sense—as in the statement in Chapter IV, Hints for Home Nurses: “Drugs in ‘candy’ form have no place in a home where there are children;” and with humor—as when he says in Chapter VI, Getting Ready for Release, that the four postdisease ingredients for disinfecting the sickroom should be: “Hot soapy water, sunshiny fresh air, elbow grease and horse sense.” He attacks the old superstitions, calls caution at the undisciplined use of new medical weapons and admits the limitations in contemporary medical knowledge.

In passing we would say that the index will prove more useful than the chapter headings which are not completely specific. We also feel that the suggestion in the chapter, Mad Dog, that you keep your dog quarantined for a month whenever suspected of a fight, shows that Dr. Bauer has had little contact with children and family pets!

Otherwise we find this an enlightening contribution to the field of popularized modern health knowledge. V. C.

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RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc., F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, Univ. of Manitoba; Biochemist, Winnipeg General Hosp., etc. Fifth Ed. Pp. 415; 73 figs. (3 plates). Philadelphia: Blakiston, 1945. Price, \$5.00.

THIS volume conforms to the general plan of these “Recent Advances” about which we have previously expressed ourselves in these columns. It “presents an up-to-date study of endocrinology . . . Considerable attention is given to the clinical aspects of the subject . . . In spite of the war . . . important advances from many countries have been taken into consideration by the author . . . The progress of chemistry makes it possible to isolate several of the ‘internal secretions.’ We have learned the chemical nature of these compounds and considerable about their physiologic activities. The logical treatment of conditions in the light of our new advance knowledge is indicated and the matter of correct therapeutic doses is discussed. Roentgen ray therapy has also been given attention. Among the outstanding advances discussed may be mentioned the following: Use of radioactive iodine; iodized proteins; function of parathyroid hormone and control of excretion of phosphat; steroid hormones of the adrenal cortex; new synthetic compounds with estrogenic activity; the posterior pituitary hormone; Cushing’s syndrome; Fröhlich’s syndrome; Simmonds’ disease differentiated from anorexia nervosa; renin of the kidney, a hormone,” etc. E. K.

**MALARIA: Its Diagnosis, Treatment and Prophylaxis.** By WILLIAM N. BISPHAM, Colonel, U. S. Army, Retired. Pp. 197. Baltimore: Williams & Wilkins, 1944. Price, \$3.50.

ACCORDING to the preface of this book, its purpose is "to give the physician a knowledge of the clinical features of malaria." Colonel Bispham apparently intended a masterly treatise, for he enlisted the aid of no less than 12 well-known and respected authorities, each of whom is said to have reviewed sections of the book. Some seem to have done so, judging from variations in the text. Others were perhaps too busy or too kindly to be justly critical. The result is a very uneven, rambling sort of discourse. It contains nothing new and much that is outmoded. Only 41 of its 175 pages are concerned with the clinical features of malaria. The remainder is taken up with history, geographic distribution, immunity, prevention, and other phases of the subject. The book cannot be recommended. H. R.

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**FAMILIAL SUSCEPTIBILITY TO TUBERCULOSIS.** By RUTH RICE PUFFER. Pp. 106; 9 figs. and 21 tables. Boston: Harvard Univ. Press, 1944. Price \$2.00.

THE purpose of this monograph is to present evidence relative to the rôle of familial susceptibility and exposure to the infection in the development of tuberculosis. The author reviews some of the outstanding experimental and epidemiologic studies which deal with these two factors not only in tuberculosis but also in leprosy, rheumatic fever, poliomyelitis and diabetes. The data accumulated from an intensive study over a 10-year period of the families of 541 white index cases in Williamstown County, Tenn., are summarized and evaluated.

Among the important observations detailed, the following may be noted. The incidence of the disease among siblings of tuberculous individuals was about twice as great as among siblings of the non-tuberculous consorts of these index cases, the control group. Likewise the tuberculosis mortality was greater in the former group. The varying and often contradictory reports in the literature relative to the incidence of the disease in consorts of tuberculous patients finds an explanation in Puffer's data for she found that consorts whose siblings are tuberculous develop the disease more frequently than consorts whose families are less affected by the infection. Data pointing in the same direction are given for parents and children of tuberculous cases. In all these instances the author is quite aware that it is often difficult to evaluate which of the two factors, susceptibility or exposure, plays the greater rôle. It is clear, however, that the data presented do lend weight to the concept that hereditary factors play a significant rôle in the disease.

Hence in any program for the control of tuberculosis it is not enough to examine all contacts of a tuberculous individual, it is also imperative, Puffer maintains, to investigate all the blood relatives of the tuberculous individuals in order to ferret out the tuberculous cases. She stresses the need of investigation of the factors underlying congenital resistance to the infection.

The book is an important contribution to the subject, is well written, comprehensively visualized and restrained in its conclusions. M. L.

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**CHILD CARE AND TRAINING.** By MARION L. FAEGRE and JOHN E. ANDERSON. Sixth Ed. Pp. 320; with ills. Minneapolis: Univ. of Minnesota Press, 1944. Price, \$2.50.

THE first two chapters summarize physical development in cursory fashion, but the bulk of this easy-to-read, excellent book deals most intimately and helpfully with the growth of the normal child's intelligence, emotions and behavior responses. It may be recommended to parents—and doctors—who feel the need of experienced counsel for child rearing problems at home.

I. W.

**ARTERIAL HYPERTENSION.** Its Diagnosis and Treatment. By IRVINE H. PAGE and ARTHUR CURTIS CORCORAN. Pp. 352. Chicago: Year Book Publishers, 1945. Price, \$3.75.

IN 352 well-written pages the authors have clearly presented their ideas on the diagnosis and treatment of arterial hypertension. They are entitled to speak with authority on a subject about which they have worked, and thought, and written so much. That the book is still somewhat unsatisfying is not the fault of the authors but rather the result of the present unsettled state of the general problem of hypertension. Research workers in this field may be disappointed at certain omissions; for example, the endocrine system is given scant attention. One feels, however, that these omissions are intentional, and are part of the authors' plan in separating the wheat from the chaff, as they see it. For the clinician, the book offers a sincere, humane and well-integrated guide that should serve him well. The authors are to be congratulated especially upon their choice of the title "arterial hypertension" instead of the more generally used term of "high blood pressure." After all, the ordinary sphygmomanometer measures the arterial pressure only, and indirectly at that.

J. G.

**LEAD POISONING.** By ABRAHAM CANTAROW, M.D., Associate Professor of Medicine, Jefferson Medical Coll.; Assistant Physician and Biochemist, Jefferson Hosp., Philadelphia; and MAX TRUMPER, Ph.D., Lt. Col., H-V (S), USNR., Naval Medical Research Inst., Bethesda, Md.; formerly Lecturer in Toxicology, Jefferson Medical Coll.; Consultant in Industrial Toxicology, Cynwyd, Pa. Pp. 264. Baltimore: Williams & Wilkins, 1944. Price, \$3.00.

THE volume points out that lead poisoning, almost exclusively an occupational disease, with the exception of a small percentage of cases occurring in infants and young children, is probably the most prevalent industrial poisoning. The metal enters the body most commonly through the gastro-intestinal and respiratory tracts, occasionally through the skin (tetra-ethyl) and, rarely, from the subcutaneous tissues. Regardless of route of absorption or chemical or physical form, the primary distribution in the tissues is essentially the same, the bones eventually containing practically the entire deposit. There is a striking similarity of behavior of lead and calcium as regards their deposition and mobilization from bones. Lead is eliminated largely in feces and urine, and has been found in milk. High values for lead in the blood, urine and feces indicate only undue exposure, and must be correlated with the clinical picture before the diagnosis of lead poisoning can be made. Symptoms may first appear years after the last exposure, due to mobilization of the stored metal. Lead poisoning may be acute or chronic, the latter being encountered most frequently clinically. Development is characteristically insidious. Prominent clinical manifestations are gastro-intestinal symptoms, mild anemia and palsies. Recent studies indicate that the fundamental lesion of lead paralysis is in disturbed muscle physiology. Other significant findings are a lead line, and signs and symptoms of hypertensive encephalopathy.

The authors are convinced of "the necessity for a more general appreciation of the extent of the lead hazard and the importance of the early recognition of chronic lead poisoning." They have culled from an enormous literature material representing authoritative opinion, and on controversial questions have expressed a personal preference based on their own experience. There is some repetition, and at times the data of various investigators is so conflicting as to weaken any definite conclusion; but on the whole the 264 page book is very useful for reference work, and for those interested in a detailed knowledge of the subject. It covers in a thorough manner: (1) absorption, transportation, deposition and excretion of lead; (2) pathology and pathologic physiology; (3) clinical manifestations; (4) lead in blood, body fluids and excretions; (5) treatment of lead poisoning; (6) occurrence of chronic lead poisoning; (7) lead products in industry; (8) procedures for determination of lead.

N. A.

## NEW BOOKS

*The Trials and Triumphs of the Surgeon.* And Other Literary Gems. By J. CHALMERS DA COSTA, M.D., LL.D. Edited by FREDERICK E. KELLER, M.D. Pp. 401; no ills. Philadelphia: Dorrance, 1944. Price, \$5.00.

*The Abortion Problem.* Proceedings of the Conference Held under the Auspices of the National Committee on Maternal Health, Inc., at the New York Academy of Medicine, June 19 and 20, 1942. By HOWARD C. TAYLOR, JR., M.D., Conference Chairman. Pp. 182; 3 ills. Baltimore: Williams & Wilkins, 1944.

*Segmental Neuralgia in Painful Syndromes.* By BERNARD JUDOVICH, B.S., M.D., Instructor in Neurology, Graduate School of Medicine, Univ. of Pennsylvania; Clinical Instructor in Neurology, Women's Medical Coll.: Chief of Neuralgia Clinics, Philadelphia General Hosp., Graduate Hosp., and Women's Medical Coll. Hosp., Philadelphia; and WILLIAM BATES, B.S., M.D., F.A.C.S., F.I.C.S., Professor of Surgery, Graduate School of Medicine, Univ. of Pennsylvania; Consulting Surgeon, Babies Hosp. and Philadelphia Home for Incurables; Consulting General Surgeon, Wills Hosp., Philadelphia. Pp. 313; 178 ills. Philadelphia: Davis, 1944. Price, \$5.00.

*A Textbook on Pathology of Labor, the Puerperium and the Newborn.* By CHARLES O. MCCORMICK, A.B., M.D., F.A.C.S., Clinical Professor of Obstetrics, Indiana Univ. School of Medicine; Consulting Obstetrician to William H. Coleman Hosp. for Women, Indianapolis City Hosp., and Sunny Side Sanitarium. Pp. 399; 191 ills. St. Louis: Mosby, 1944. Price, \$7.50.

*The Story of a Hospital.* The Neurological Institute of New York 1909-1938. By CHARLES A. ELSBERG, M.D., Chief of the Surgical Service (Emeritus), Neurological Institute, New York. Pp. 174; numerous ills. New York and London: Hoeber, 1944. Price, \$3.50.

THIS is "a short account of the Neurological Institute from its simple beginnings in a small building to its more mature activities in the large and luxurious quarters at the Columbia University Medical Center. To the facts gathered from the records of the Board of Trustees and of the Medical Board, there has been added some notes from Dr. Elsberg's records." This booklet was written to "serve as a permanent record of the activities of a small group of medical pioneers."

*Anatomy.* As a Basis for Medical and Dental Practice. By DONALD MAINLAND, M.B., Ch.B., D.Sc., F.R.S.E., F.R.S.C., Professor of Anatomy, Dalhousie Univ., Halifax, N. S., Canada. Pp. 863; no ills. New York: Hoeber, 1945. Price, \$7.50.

*Duodenal and Jejunal Peptic Ulcer.* Technic of Resection. By RUDOLF NISSEN, M.D., Attending Surgeon, Jewish Hosp. of Brooklyn; Member, Medical Advisory Board, National Jewish Hosp. of Denver; formerly Professor of Surgery and Head of Dept. of Surgery, Univ. of Istanbul; and Associate Professor of Surgery, Univ. of Berlin. Foreword by OWEN H. WANGENSTEEN, M.D., Ph.D., Professor of Surgery, Univ. of Minnesota; Surgeon-in-Chief, Univ. of Minnesota Hosp. Pp. 143. New York: Grune & Stratton, 1945. Price, \$4.75.

*Studies of Burns and Scalds.* Medical Research Council. By L. COLEBROOK, T. GIBSON, J. P. TODD, A. M. CLARK, A. BROWN, and A. B. ANDERSON. Pp. 204; many figs., charts and tables. London: His Majesty's Stationery Office, 1944. Price, 4s. 0d. (about 80 cents).

*The Medical Clinics of North America.* Chicago Number. Symposium on Neuropsychiatric Diseases. Pp. 271; 44 figs. Philadelphia and London: Saunders, 1945. Sold only by the year (\$16.00).

*A Laboratory Guide in Chemistry.* By JOSEPH H. ROE, Ph.D., Professor of Biochemistry, The School of Medicine, George Washington Univ., Washington, D. C. Pp. 191. St. Louis: Mosby, 1944. Price, \$1.00.

## NEW EDITIONS

*A Text-book of Psychiatry* for Students and Practitioners. By D. K. HENDERSON, M.D. (EDIN.), F.R.Fac. P. & S. (GLAS.), F.R.C.P.E., Physician-Superintendent of The Royal Edinburgh Hosp. for Mental Disorders, and Professor of Psychiatry, Univ. of Edinburgh; and R. D. GILLESPIE, M.D. (GLAS.), F.R.C.P. (LOND.), D.P.M. (LOND.), Physician for Psychological Medicine, Guy's Hosp., London; formerly Examiner in Mental Diseases and Psychology in the Univ. of London; Acting Air-Commodore, Royal Air Force Volunteer Reserve. Sixth Ed. Pp. 719. New York: Oxford Univ. Press, 1944. Price, \$7.00.

*Microbiology and Pathology*. By CHARLES F. CARTER, B.S., M.D., Instructor in Microbiology and Pathology, Parkland Hosp. School of Nursing, Dallas, Tex.; Director, Carter's Clinical Laboratory, Dallas, Tex.; Consulting Pathologist, St. Louis Southwestern Railway Hosp., Texarkana, Ark.; Consulting Pathologist, Mother Frances Hosp., Tyler, Tex.; formerly Director of Laboratories, Parkland Hosp. Third Ed. Pp. 777. St. Louis: Mosby, 1944. Price, \$3.50.

THIS book, not so small as it looks, contains an amazing amount of information on various aspects of Microbiology and Pathology. Those who do not ask for much will not be disappointed. Though the words "for nurses" have been omitted from the title, the purpose remains. True-false questions at the ends of many chapters add a spice of novelty. The colored illustrations on coated paper are excellent, many black-and-whites on war paper had better have been omitted entirely.

*Recent Advances in Endocrinology*. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hosp. Fifth Ed. Pp. 415; 73 figs., including 3 plates. Philadelphia: Blakiston, 1945. Price, \$5.00.

*Clinical Case-taking. Guides for the Study of Patients*. By GEORGE R. HERRMANN, M.D., Ph.D., Professor of Medicine, Univ. of Texas. Third Ed. Pp. 192. St. Louis: Mosby, 1945. Price, \$1.75.

*Principles of Chemistry*. An Introductory Textbook of Inorganic, Organic and Physiological Chemistry for Nurses and Students of Home Economics and Applied Chemistry. By JOSEPH H. ROE, Ph.D., Professor of Biochemistry, School of Medicine, George Washington Univ.; formerly Instructor in Chemistry, Central School of Nursing, Washington, D. C. Sixth Ed. Pp. 403; 47 figs. (4 color plates). St. Louis: Mosby, 1944. Price, \$2.75.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1945

## ORIGINAL ARTICLES

### A SEVERE TYPE OF HEREDITARY ANEMIA WITH ELLIPTOCYTOSIS

#### INTERESTING SEQUENCE OF SPLENECTOMY

BY THOMAS B. COOLEY, M.D., Sc.D.

DETROIT, MICH.

THESE cases seem worth reporting for two reasons: the facts that no similar cases appear in the literature, and that there seems to have been an unusual effect of splenectomy in one of the patients.

**Case Histories.** The subjects of this report are 2 brothers, Jerome and Robert C., coming from a family whose disease history is shown by the family tree in Figure 1. In the 5 generations of which we have record, 19 out of 29 boys born to women in the mother's line of descent have developed a severe anemia. Of these, 16 have died—10 in their first year; one is said to have recovered, and the other 2 are our present patients. No girls have been affected.

The parents' bloods are negative in this generation: the transmission has always been through the unaffected mother. The type of heredity here would seem at first glance to be the same sex-linked type as in hemophilia, but another type, the "sex-influenced" heredity whose common example is pattern baldness, cannot be ruled out on the data we have, and considering information that we have on other patients with elliptocytosis is perhaps the more probable. This type is not dependent on the sex chromosomes, and is recessive in the female and dominant in the male. It can be transmitted by the father directly to his sons. It cannot be distinguished from the sex-linked type in a family like this in which no affected males have lived to have children. (I am indebted to Prof. L. H. Snyder for reminding me of the possibility of sex-influenced heredity here.)

Of these 2 boys, Jerome, the younger, born March 15, 1935, is the more seriously affected, because of susceptibility to respiratory infections which apparently are the cause of exacerbations of the anemia and necessitate frequent transfusions. Robert, born June 23, 1931, lives comfortably on an average hemoglobin of about 7 gm., is able to take part in the ordinary activities of boys of his age, and was supposed by his family to be in normal health until he was brought in with the other children for blood studies. Most of our data come from our study of Jerome, with Robert serving for comparison since he has what might be looked on as the natural uncomplicated course of the condition.

Jerome was first seen in our clinic on April 5, 1941, having been referred from an out-state hospital where he had recently received 2 transfusions. He had been known to be anemic almost since birth, and had been the recipient



of a variety of ineffective medicaments, but need for transfusion had not been recognized before the present episode. On examination he seemed definitely stunted, weighing less than 40 pounds at 6 years, and exhibited the pallor of a severe anemia without jaundice. He had a slight "hemic" murmur; his spleen was neither palpable nor enlarged to percussion, and there was no indication of liver enlargement. There was no lymphadenopathy. Roentgen ray films of the skeleton showed nothing remarkable. Blood studies showed: Hb., 3.4 gm.; R.B.C., 3.53 million; marked fragmentation; extreme hypochromia; fragility, 0.48 to 0.20 (wide resistance span); quantitative urobilin, 0.69% (34% direct, 58% prompt); no reticulocytes were seen. More than 50% of the erythrocytes were elliptical (Fig. 2). The white cell count was 5100, with normal differential. The urine and stools were negative.

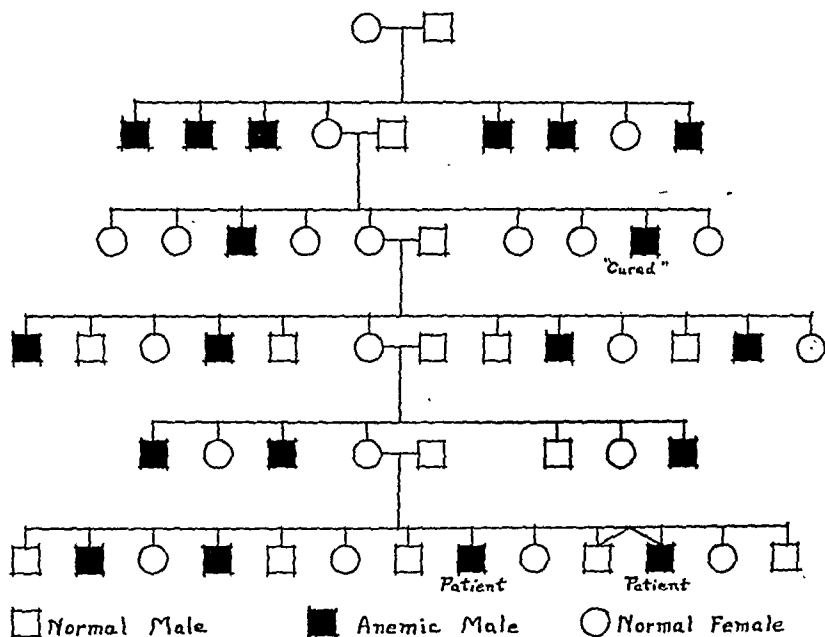


FIG. 1.—Mrs. C's. descent in the female line, which originated in Holland.

Robert was brought in 3 days later for blood study, together with 6 out of 8 siblings, 4 brothers and 2 sisters, all of whom had normal blood, with regard both to anemia and to the presence of elliptocytes. Robert's blood smear resembled Jerome's so closely that it was nearly impossible to distinguish between them; though his hemoglobin was 6.6 gm., there was not the marked fragmentation observed in Jerome's blood, and the blood bilirubin was 0.41%.

Some characteristics of the erythrocytes in these bloods deserve special note, as they differ somewhat from those illustrated in other case reports of "elliptocytic anemia." The most noticeable form in these two bloods is the "sausage" cell, of which there is a high percentage, though at the same time there are many cells recognizable as elliptocytes only as close inspection shows one diameter to be greater than the other. "Pencil cells" are not prominent, nor is the division by median fission so marked as in some types of elliptocytes. A very striking characteristic of the cells, and perhaps the most important, is an appearance of hemoglobin deposition at the periphery of the cell, with complete absence of stain in the center. This "signet ring" appearance has always been prominent in the blood of both boys, and together with the behavior of their counts and the knowledge that there was ample available iron has led us to the belief, to which I shall return later, that the cause

of the anemia lay in an inability to synthesize hemoglobin beyond a certain point. One of my friends said, when this characteristic was described to him, "Whenever the hemoglobin reaches a certain point something seems to put on the brake," which was a good statement of our own opinion of what was happening.

We have observed these 2 boys for more than 3 years. Two other features of their bloods have interested us in addition to those already mentioned. These are the rather frequent occurrence of polycythemia without corresponding rise in the hemoglobin level, and a wide resistance span (*i. e.*, increased maximal resistance with normal or decreased minimal resistance) without the appearance of target cells, which have been supposed to be an explanation for it. As for the polycythemia, Robert has had a number of counts around 6,000,000 and one of 6,500,000, with Hb. in the neighborhood of 7 gm. Jerome's

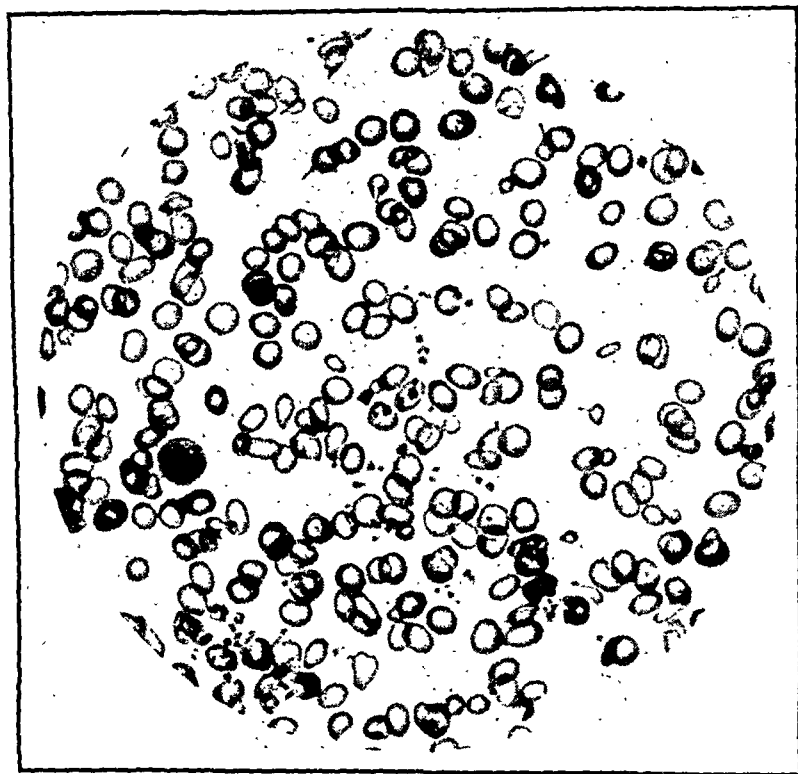


Fig. 2.—Robert C's. blood. There was no perceptible difference between the two bloods. This happens to be our best photograph.

highest count was 6,550,000 and Hb. 6.9 gm. Unfortunately the record does not show hematocrit determinations at these times. This tendency to polycythemia is noticeable in several other reports of elliptocytosis, and implies, of course, a pronounced microcytosis even though the hematocrit reading is lacking.

In February, 1942, a sternal marrow biopsy was performed upon Robert by Dr. W. W. Zuelzer, pathologist. His report (based on the study of both fresh and stained material) describes a cellular marrow in which no abnormalities were observed in cells in the erythroblast or normoblast stages. "The mature erythrocytes are often peculiar in appearance with many elongated and needle-shaped forms. There is also marked variation in the size of the erythrocytes and most of the cells which are not needle-shaped or elliptical in sections appear unusually small." His conclusion reads, "The main

abnormality appears to lie in the appearance and shape of the mature red cells. In the nucleated precursors of these cells, however, no anomalies can be demonstrated in stained sections, and the anomalies of the mature cells are probably better demonstrated in fresh preparations and blood smears than in fixed tissue."

This report adds confirmation to the observation already reported by several writers that the erythrocytes do not take on the elliptical form until just before entering the circulation.

In the course of our studies, Jerome has been the subject of numerous diagnostic and therapeutic tests. His condition was clearly a microcytic, hypochromic anemia of a type which ordinarily would be expected to respond to iron therapy, or perhaps to iron and liver. These drugs, given singly and in various combinations, elicited no response. No reticulocyte rise was ever observed following any of them. In order to eliminate the possibility of failure of iron absorption he was given, in the late spring and early summer of 1942, a series of intravenous injections of colloid iron with no more effect than the oral administration. In July of that year Dr. Carl V. Moore was kind enough to determine for us the boy's serum iron. His report reads: "the serum iron value was 0.246 mg. per 100 cc. . . . (normal average range for humans is from about 0.060 to 0.180). The only time we have obtained a level as high as 250 micrograms in serum is in pernicious anemia in relapse, in aplastic anemia and with active hemolysis such as occurs with phenylhydrazine therapy in polycythemia. There can be no doubt, therefore, that your boy has an adequate amount of iron and is able, furthermore, to mobilize it from the storehouses. I think the high serum iron means definitely that this youngster is not able to synthesize hemoglobin from iron in the bone marrow." This finding added confirmation to our conclusion, already mentioned, that we were dealing with a form of hypoplasia involving almost exclusively the hemoglobin synthesis. Tests for other possible reasons for an anemia of this type all gave negative results. Occult blood loss was suggested, but nothing of the kind could be found. A hemolytic process was apparently ruled out by the low blood bilirubin value, though the increased fragmentation during relapses was suggestive of this as an additional factor. Considering possible causes for such a hypoplastic state, we were led at once to think of the spleen, which has been suspected by a number of writers of exerting an inhibitory effect on marrow function in the presence of various diseases. Our patient was losing ground, all other therapy had proved futile, and it was finally decided to recommend splenectomy. The parents were slow to consent, but the operation was finally performed on May 25, 1943. The spleen was found to be very large and tied firmly by adhesions under the dome of the diaphragm. This accounted for the fact that we had not been able to detect the enlargement by palpation or percussion; it also had caused surgical difficulties which prevented obtaining blood specimens from the splenic vein as we wished.

*Histology of Spleen* (Dr. W. W. Zuelzer). It weighed 336 gm. (average normal, 69 gm.). There were no marked variations from normal in the architecture and no increase in fibrous tissue. There were a number of areas of extramedullary hematopoiesis, and it was in the young erythrocytes in these areas that the most striking picture was observed, both in sections and better in imprints stained with Giemsa. There were many cells smaller than normal, and of these a large proportion were elongated or elliptical in shape. These cells were remarkable in that there was a large number, even with no trace of nucleus or nuclear fragments, as well as many cell fragments, which showed no eosin stain whatever, the cytoplasm staining a delicate blue with a pale center. Erythrophagocytosis was observed only rarely. Dr. Zuelzer's conclusion is "Extramedullary hemopoiesis and hyperplasia of spleen. The material suggests formation of red cells which are deficient in hemoglobin as well as abnormal in shape and tend to be fragmented in the spleen."

The immediate effect of the operation was rather surprising. There was a temporary rise in hemoglobin, of brief duration and probably due to massive transfusions preparatory to operation. The unexpected thing was a definite

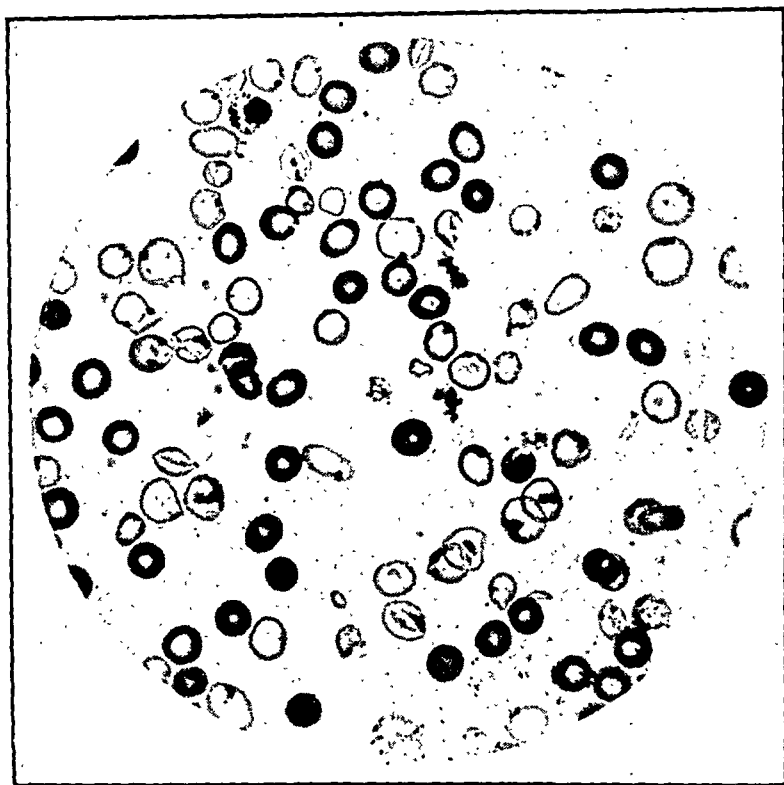


FIG. 3.—Jerome's blood 3½ months after splenectomy. Note two different types of cells.

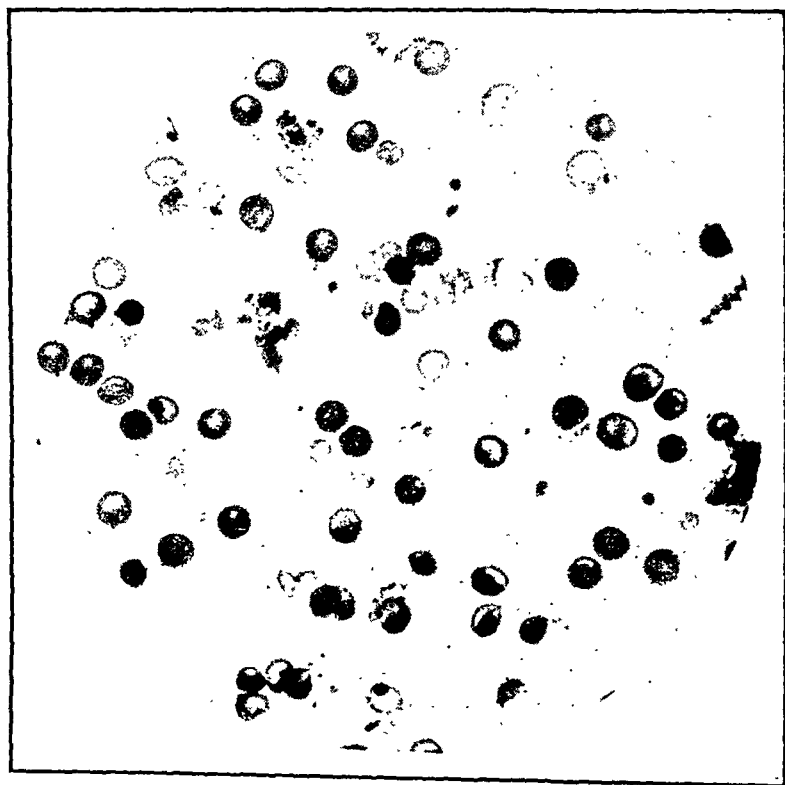


FIG. 4.—Jerome's blood 9 months after splenectomy: 104 days after last transfusion.

tendency to diminution of the proportion of elliptocytes to round forms and an apparent increase in the number of pale blue staining cells without hemoglobin. Both of these tendencies were observed almost immediately after the operation, and continued until the date of the photograph in Figure 3, in which may be noted not only the many round cells without hemoglobin, but a remarkable number of Howell-Jolly bodies. After this date followed a period of apparent improvement in the appearance of the cells. Figure 4, from a smear made in February, 1944, seems to show a fairly high percentage of cells with a reasonable amount of hemoglobin, contrasted with the cell shadows still to be seen. It would be natural to suppose that the more normal appearing cells might be donor's cells surviving from a previous transfusion, but the fact that the last transfusion was 104 days before seems to preclude this possibility. The appearance of improvement in the smear was deceptive, however, as the Hb. was only 5.4 gm., hematocrit 19.8, and reticulocytes 0.5%. No erythrocyte count was made that day, but on the following day, following transfusion of 285 cc. (red cells from the A.R.C.), it was only 1,960,000.

After this date in February we lost sight of the boys until May, as the parents took them to another clinic. Here Jerome apparently received no other treatment than transfusion. When we saw him in the middle of May the improvement in the appearance of his erythrocytes seemed to be continuing, and his Hb. had reached 11.3 gm. (last transfusion early in April). A week later it was 10.9 gm. This looked like the beginning of permanent improvement; but on a recent visit to the clinic after an absence of several weeks he was found to have Hb. 4.4 gm., R.B.C. 1,720,000, W.B.C. 16,000, and reticulocyte count 8.8%. Dr. Zuelzer found that he still had the extremely pale, shadow-like cells with Howell-Jolly bodies on the one hand and fairly normal appearing cells on the other with no transition between the two types. This examination is the only one we have showing a reticulocyte increase.

**Comment.** Two questions in connection with these cases have seemed to me of considerable interest. The first one is the probable relation of the elliptical cells to the anemia, the second the effect of Jerome's splenectomy. The elliptocytosis here is of course not the dominant hereditary type described by Dresbach and the subject of a number of articles in recent years. There is no general agreement as to whether that type ever has any essential connection with anemic states. If it has, it is most commonly with a condition distinguished from congenital hemolytic icterus only by the cell anomaly. The elliptocytes in our cases are unquestionably pathologic, but are not to be thought of as "poikilocytes" in the proper sense of that term. Elliptical cells are often seen in blood displaying marked poikilocytosis, together with misshapen cells of many other forms, but here they are the only conspicuous example of deformity. There are a good many reports in the literature of cases of anemia with similar cells, especially by Italian writers, but often no evidence of heredity is adduced, and no such effect of splenectomy has been described as in our case.

It has several times been suggested that the elliptocytosis may be an effect rather than a primary element of the anemia. The return of many cells to the round form after splenectomy might be taken as evidence for this view if one were a subscriber to the plausible theory

advanced by Dameshek and others that some splenic effect is responsible for the spherocytes of hemolytic anemia. In that case, I think one could account for the two wholly different types of cells in Jerome's recent blood pictures by supposing that the hematopoietic apparatus of the whole body was involved in the process, and that removal of the spleen remedied only that part of it. This explanation offers a reasonable analogy to what is occasionally observed in other conditions which are benefited but not finally cured by splenectomy.

One more comment seems worth making. This anemia adds one more to the list of the "refractory" anemias, uninfluenced by any form of therapy, except occasionally by splenectomy, and it is noteworthy that, so far as I know, all of these refractory anemias are due to fundamental constitutional defects in the hematopoietic system. Sick cell anemia, Mediterranean anemia and a familial anemia reported by Strauss and Daland, are other examples. This last, judging from the microphotographs accompanying the report, is also characterized by elliptocytes.

**Summary.** I have described an anemia observed in 2 brothers, whose family history indicates that the disease is transmitted by unaffected females in the "sex-linked" manner of hemophilia, or the "sex-influenced" manner of pattern baldness, between which it is not possible to distinguish on present information. Both of the brothers exhibit in their blood a striking type of elliptocytosis, which is not found in any of the numerous siblings nor in either parent. Of our 2 patients, Robert, the elder, has never shown indications of serious illness, but lives very comfortably on average hemoglobin of 7.8 gm., while Jerome, the younger, has always been more or less of an invalid, stunted, pale, and subject to rather frequent exacerbations of his anemia in which transfusions become necessary. He has had somewhat more than 20 such periods during our 3 years observation of him. Both Jerome's progress and the family history tend to give a somewhat exaggerated impression of the gravity of the fundamental anemia—in Jerome's case because of these secondary lapses, and in the cases of the other children who died because of inadequate therapy, which did not in any case include transfusion.

The blood of both boys has tended to be microcytic and hypochromic, and each has had periods of polycythemia with counts above 6,000,000. Jerome's frequent relapses have apparently been due to infection, and the fact that at these times his blood shows marked fragmentation makes it seem probable that there is a hemolytic element present, though this could be proved only by determinations of total pigment excretion which we were not prepared to make. His episodes of respiratory infection are described by his parents as asthmatic. We suspected bronchiectasis, but failed to demonstrate it by Roentgen ray. They are probably bronchitis. As his parents, who live a long way from the hospital, keep him at home during these periods, we have no definite knowledge of their character. His white cells when we have seen him immediately following a relapse have usually shown a high neutrophil count, above 20,000.

There was no doubt in our minds that the striking change in Jerome's cells was due to the splenectomy. Robert's cells have not at any time shown anything similar. We believe that the operation influenced favorably the fundamental disease process, and that if by suitable prophylaxis we can minimize the infectious element we may hope for something approaching a cure.

## THE FREQUENCY OF THALASSEMIA

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In 1942 Wintrobe,<sup>13</sup> commenting on the frequency of thalassemia (Cooley's anemia, erythroblastic anemia, Mediterranean anemia), wrote that "the disease is rare, apparently, for less than 100 cases have been reported since Cooley's paper appeared in 1925." Recently we have collected data indicating that the disease is more common than the number of published reports would indicate. As is well known, the condition is largely confined either to peoples now living on or near the shores of the Mediterranean—Greeks, Italians, Syrians, Armenians—or to those whose ancestors lived there until recent times. This report is an attempt to estimate the incidence of the condition in one specific group derived from the Mediterranean region, namely, individuals of Italian descent residing in the city of Rochester, N. Y. These individuals are for the most part either immigrants from Sicily and southern Italy or the descendants of such immigrants, and so represent a relatively homogeneous element. Such an estimate not only has some medical interest but is basic to an estimation of the frequency of a related but milder anemia to be discussed below.

Table 1 summarizes the known cases of thalassemia occurring in individuals of Italian descent born in the city of Rochester, N. Y., between 1928 and 1942 and admitted to the various hospitals of this city. The year 1928 has been arbitrarily chosen as the beginning point in this series because, although the disease was first described in 1925, a certain lag in the general recognition of the condition is unavoidable. The year 1942 has been chosen as the last year because cases are often not recognized prior to 1 year of age, so that some cases born subsequent to this date may not yet have come to the attention of a physician. We are very grateful to the various hospitals of this city for their coöperation in permitting us to examine their records of cases of thalassemia. Eleven individuals with the disease are known to have been born in this city over the 15-year period. This figure is probably a minimum estimate of the number of cases, since some individuals

may go undiagnosed and die at an early age of intercurrent infection, to which they are very susceptible.

TABLE 1.—CASES OF THALASSEMIA BORN IN ROCHESTER BETWEEN 1928 AND 1942 AND DIAGNOSED IN THE VARIOUS HOSPITALS OF THE CITY

Hospital	No. of cases
Strong Memorial and Rochester Municipal Hospitals . . . . .	5
The Genesee Hospital . . . . .	3
Rochester General Hospital . . . . .	2
Highland Hospital . . . . .	1
St. Mary's Hospital . . . . .	0*
Park Avenue Hospital . . . . .	0

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\* The case described by Flynn<sup>6</sup> from St. Mary's Hospital was not a native of Rochester.

Rochester has a relatively large Italian population. At the time of the 1930 census, there were 23,935 individuals in Rochester who were born in Italy, and 31,478 first generation native whites born of Italian or mixed Italian parentage.<sup>2</sup> The 1940 census figures are less useful, since the number of first generation Italians is not listed; the number of persons born in Italy is given as 20,929.<sup>3</sup> The number of second generation Italians can only be approximated; various approaches lead to an estimate of an average of 20,000 living in this city between 1928 and 1942. These figures lead to the estimate that in the years 1928-1942 there was an average of approximately 75,000 individuals Italian born or of Italian descent in this city. Maller,<sup>8</sup> on the basis of the 1930 census figures and vital statistics data for 1930 secured from the Department of Health of New York City, found that the mean birth rate for 15 Italian areas in New York City for the year 1930 was 23.15 per 1000. The birth rate is probably not greatly dissimilar in the Italian areas of Rochester. Over the 15-year period from 1928 to 1942 one can, on the basis of these figures, reasonably estimate the number of children born of Italian parentage as 26,044. The incidence to thalassemia is therefore approximately 1 in 2368 births, or 0.00042. Stevens<sup>10</sup> has pointed out that when dealing with such small fractions, one cannot employ the usual formula for estimating the error of a proportion ( $\sqrt{p(1-p)/n}$ ) but should use a method, which he describes, based upon an expansion of the binomial series. By this latter method, the probability is 19 in 20 that the "true" frequency of thalassemia lies between 0.00021 and 0.00076. This method makes allowance for differences between the observed and the "true" frequency due to the sampling technique, but does not, of course, take into account possible inaccuracies in the estimate due to differences between the actual and estimated size of the Italian element and its birth rate.

In 1940 and 1941 three groups of investigators<sup>4,11,14</sup> independently described a new type of familial, iron-resistant, hypochromic, microcytic anemia occurring in individuals of Italian descent. They pointed out that this anemia was qualitatively similar to thalassemia but was quantitatively much less severe in that it lacked the degree of red cell imperfection and circulating erythroblasts. Wintrobe<sup>13</sup> subsequently showed that both the parents of 2 individuals suffering from thalassemia



had this similar but milder anemia. Dameshek<sup>5</sup> and Smith<sup>9</sup> confirmed this observation and also found the milder condition in siblings of individuals with thalassemia. A number of theories as to the mode of inheritance and relationship of these two anemias were promulgated. The present authors have elsewhere<sup>12</sup> reviewed these theories and found that the available data are best fitted by the hypothesis, first suggested in incomplete form by Caminopetros,<sup>1</sup> that thalassemia is due to homozygosity for an inherited factor, and that the similar, milder disorder is due to heterozygosity for the same factor. In other words, there is, according to genetic hypothesis, a factor which when represented once in the germ plasm results in the mild anemia; when represented twice, in thalassemia. In view of the peculiar etiologic relationships between these two anemias, we<sup>12</sup> have suggested the term "thalassemia major" for full-blown thalassemia, and "thalassemia minor" for the milder disorder.

As yet no direct surveys of the frequency of thalassemia minor in individuals of Italian descent are available. However, given an hereditary mechanism such as has been postulated, the frequency of thalassemia minor can readily be calculated once the frequency of thalassemia major is known. If we let  $A'$  represent the inherited factor responsible for thalassemia, and  $A$  its normal allelomorph, then with respect to these factors adult Italians are of two types,  $AA$  (normal) and  $A'A$  (thalassemia minor). The homozygote  $A'A'$ , showing thalassemia major, with rare exceptions dies before the age of reproduction. Let  $x$  be the frequency of  $AA$  individuals, and  $y$  the frequency of  $A'A$ . Assuming random mating and equal fecundity for both types, the various possible marriages would occur with the frequencies and results shown in Table 2. The frequency with which children with thalassemia major appear in the Italian population is  $\frac{y^2}{4}$ . Since the incidence of thalassemia major is estimated at 0.00042, then

$$\frac{y^2}{4} = 0.00042, \text{ and}$$

$$y = 0.041.$$

This indicates that thalassemia minor occurs in approximately 1 in each 25 adult Italians. If the true frequency of thalassemia major is more nearly 0.00021 (the lower estimate given above, compatible with the data at the 5% level of significance), then the frequency of thalassemia minor is 1 in 34, while if the frequency of the major form is 0.00076 (the higher estimate given above, likewise compatible with the data at the 5% level of significance), thalassemia minor would occur in about 1 in 18 individuals. This estimate of the frequency is sufficiently high to make one wonder why the disease has gone so long unrecognized. As has been pointed out by various investigators<sup>5,12</sup> the condition is usually mild and readily confused with an iron-deficiency anemia.

The present estimates of the frequency of thalassemia major and minor can only be regarded as approximate. However, no source of

major error in the calculations is immediately apparent. No allowance is made for the effect of consanguinity on the calculations, the amount of this in the Italian community being unknown. The existence of significant degrees of consanguinity would result in a spuriously high estimate of the frequency of the mild disease. On the other hand, marriages between Italians and other racial elements in which the postulated factor is less common will decrease the incidence of thalassemia major, and hence give a spuriously low estimate of the frequency of thalassemia minor. For the present these two opposing influences are regarded as cancelling each other out in the above calculations. Elsewhere<sup>12</sup> we have pointed out an apparent excess of thalassemia minor in marriages between normal individuals and those with thalassemia minor; this fact does not influence the calculations.

TABLE 2.—THE RESULTS OF RANDOM MARRIAGE IN A POPULATION CONTAINING THE GENOTYPES AA AND A'A IN THE FREQUENCY  $x$  AND  $y$

Marriage	Frequency of marriage	Type and frequency of offspring
AA × AA . . . . .	$x^2$	$x^2$ AA
AA × A'A . . . . .	$2xy$	$xy$ AA : $xy$ A'A
A'A × A'A . . . . .	$y^2$	$\frac{y^2}{4}$ AA : $\frac{y^2}{2}$ A'A : $\frac{y^2}{4}$ A'A'

Persons having the constitution A'A' are not included in the calculations since in this case such individuals rarely reproduce.

The clinical significance of thalassemia minor has yet to be evaluated carefully. Many persons compensate for their individually deficient erythrocytes by an increased red cell count, and therefore they have approximately normal values for hemoglobin and hematocrit. Others fail to make this adjustment, and go through life with subnormal values. It seems probable that they are handicapped to the same extent as individuals with an iron-deficiency anemia of comparable magnitude (Mackay<sup>7</sup>), with the added disadvantage that this is a chronic disorder. Further studies on the clinical significance of a disease involving approximately 4% of individuals of southern Italian extraction are desirable.

**Summary.** From a survey of hospital records, the incidence of thalassemia major in the Italian element of the city of Rochester, N. Y., was found to be approximately 0.00042 (1 in each 2368 births). The incidence of the genetically related condition, thalassemia minor, was estimated to be 0.041 (1 case in each 25 persons).

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## EOSINOPHILIA FOLLOWING PARENTERAL LIVER THERAPY

### LITERATURE AND CASE REPORT

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AMONG the less well known and the less common causes for eosinophilia is the therapeutic administration of liver and liver extract. Although it was realized that eosinophilia occurred not infrequently in cases of untreated pernicious anemia,<sup>5,21</sup> following the introduction of liver therapy for pernicious anemia by Minot and Murphy,<sup>26,27</sup> a number of reports of eosinophilia as a result of treatment with liver appeared in the literature.<sup>4,11,14,29,30,34,35</sup> It early became evident, however, that eosinophilia following the use of liver was not restricted to patients with pernicious anemia, for this finding was frequently observed both in normal subjects and in patients suffering from disorders other than pernicious anemia when liver or liver extract was administered in repeated doses.<sup>1,13,20,31,32</sup> In Table 1 are summarized the cases of eosinophilia following liver therapy of various types which we have been able to gather from a careful survey of the literature to date (June 1944).

The most extensive papers on the phenomenon of eosinophilia following the therapeutic use of liver are those of Meulengracht and Holm,<sup>25</sup> Massobrio and Maranzana,<sup>23</sup> and Allin and Meyer.<sup>2</sup> In 1930, Meulengracht and Holm<sup>25</sup> studied the eosinophil count following the administration of raw liver, fried liver, and oral liver extract in a group of patients with pernicious anemia and in a control group of patients suffering from a variety of other diseases. In both groups of subjects identical changes were found. The daily administration of large doses of raw liver resulted regularly in marked eosinophilia which in 1 case reached a level of 74%. As a rule, the eosinophilia appeared rather suddenly after about 4 weeks of treatment, and it persisted as long as the administration of raw liver was maintained. In those patients who received repeated doses of fried liver or oral liver extract eosinophilia occurred only occasionally and in no instance was higher than 9%.

Massobrio and Maranzana,<sup>23</sup> in 1938, extensively reviewed the literature on the subject of eosinophilia following the ingestion of liver and added a number of case studies of their own. They found that in a series of 17 patients with pernicious anemia who were treated by the

daily administration of steamed liver eosinophilia appeared in 12 instances, reaching a level of over 20% in 2 cases; 2 of the 5 patients who showed no eosinophil response were followed for only 2 weeks. The authors observed that in the majority of instances the eosinophilia made its appearance about 4 weeks after the institution of liver therapy, although in 2 cases levels of 12 and 14% were present after only 1 week. In a group of 4 pernicious anemia patients who were treated by the

TABLE 1.—A TABULATION OF REPORTED CASES OF EOSINOPHILIA FOLLOWING THE ADMINISTRATION OF LIVER OR LIVER EXTRACT

Year	Author	No. of cases with eosinophilia*	Type of liver	Maximum range of eosinophilia	Type of subjects
1927	Watkins and Berglund <sup>24</sup>	1	Raw	48% of 10,000	P.P.A.
1928	Poulton <sup>25</sup>	1	Raw	3400 per c.mm.	P.P.A.
1928	Whitby <sup>25</sup>	4	Raw or cooked	5-26%	P.P.A.
1928	Ordway and Gorham <sup>29</sup>	1	Raw (?)	25%	P.P.A.
1928	Smith and Whitby <sup>32</sup>	11	Raw	470 to 13,000 per c.mm	Convalescents from diseases other than P.P.A.
1928	Adler and Schiff <sup>1</sup>	2	Oral extract	9%	Normals†
1928	Seyfarth <sup>31</sup>	6	Raw or slightly cooked	9-15%	Normals
		Not specified	Raw or slightly cooked	10-15%	P.P.A.
1930	Fliessinger and Laur <sup>11</sup>	1	Raw	8% of 4800	P.P.A.
1930	Griva <sup>13</sup>	8	Partly cooked	6-51%	P.P.A.
		3	Partly cooked	6-8.5%	Anemias other than P.P.A.
1930	Meulengracht and Holm <sup>23</sup>	22‡	Raw	Up to 74%	P.P.A.
		4	Raw	Up to 67%	Diseases other than P.P.A.
		1	Fried	6%	P.P.A.
		1	Fried	9%	Diseases other than P.P.A.
		2	Oral extract	8-9%	P.P.A.
1932	Lehndorff <sup>20</sup>	1	Raw	45%	Hemolytic anemia
1932	Heilmeyer <sup>14</sup>	2	Parenteral extract	15% of 10,600	P.P.A.
				19% of 8200	
1933	Barone and Costa <sup>4</sup>	3	Whole liver	10-41%	P.P.A.
1935	Corelli <sup>6</sup>	1	Whole liver orally and extract parenterally	28%	Pregnant woman with P.P.A.§
1933	Massobrio and Maranzana <sup>23</sup>	12	Steamed liver	Up to 20%	P.P.A.
		5	Raw	14-27%	P.P.A.
		3	Nearly raw	5-13%	Normal
1939	Murphy <sup>23</sup>	1	Whole liver	50% of 18,000	P.P.A.
1940	Allin and Meyer <sup>2</sup>	10	Cooked	Average 8.6%	P.P.A.
		10	Oral extract	6-10%	P.P.A.
		36	Parenteral extract	Average 11.3% (maximum 36%)	P.P.A.
		31	Mixed oral and parenteral therapy	Average 10.4%	P.P.A.
		1	Parenteral extract	7.75%	Normal
		1	Parenteral extract	9.75%	P.P.A.

\* Those cases in which eosinophilia did not develop are not included in this table.

† One dog given fresh liver and a second given liver extract orally showed mild eosinophilia.

‡ This figure may not be correct; the exact number is not set forth in the original report.

§ The new-born infant showed an eosinophilia of 5% at birth; eosinophilia was not present 2 months later, although the child was breast fed.

daily administration of liver boiled at 100° C. for 30 minutes eosinophilia did not result despite good response of the erythrocytes; 1 of these patients was later given raw liver by mouth and within 2 days developed an eosinophilia of 20%. A third series of 9 patients with pernicious anemia received liver extract parenterally for therapy, and in no instance was eosinophilia induced; 4 of this group were then given whole uncooked liver by mouth with resultant eosinophilia of from 14 to 27%. A group of 3 normal subjects was fed nearly raw

liver daily, and within 1 to 2 weeks eosinophilia of from 5 to 13% was observed in each instance and was maintained at about the maximum level as long as liver was continued. The authors found that once eosinophilia following the ingestion of liver appeared it remained as long as treatment was maintained, and that when liver therapy was discontinued the eosinophil level decreased to within normal limits in from 10 to 20 days.

Massobrio and Maranzana fed 4 dogs, in which parasitosis had been excluded, daily rations of raw liver. In each instance an eosinophilia of from 20 to 26% resulted within from 15 to 30 days. Immature and young forms of the eosinophilic granulocyte series were extremely rare in the peripheral blood, a maximum of only 3% of eosinophilic metamyelocytes having been noted. Specimens of bone marrow obtained from the animals during periods when eosinophilia in the peripheral blood was pronounced revealed no significant changes in the numbers of cells of the eosinophilic series.

Allin and Meyer,<sup>2</sup> in 1940, reviewed the records of 279 patients with pernicious anemia. Of 224 who had received liver therapy in one form or another, 87 developed eosinophilia of 4% or more of the total leukocyte count at some time during the period of observation. Eosinophilia was found in 10 of the 13 cases given cooked liver by mouth and in 10 of the 41 patients who received liver extract preparations orally. Of the 79 patients to whom liver extract was given intramuscularly, 36 showed an eosinophilia which averaged 11.3%, the maximum figure being 36%. Of the group of 91 patients who received mixed oral and parenteral therapy, eosinophilia resulted in 31. However, in the group of 55 patients who received no liver therapy eosinophilia occurred in 27 instances.

Allin and Meyer administered repeated doses of liver extract parenterally to 5 previously untreated patients with pernicious anemia and to 4 normal subjects from whom no allergic history could be obtained; mild eosinophilia developed in 1 of the normal subjects and in 1 of the pernicious anemia patients. The 9 patients making up the two groups just mentioned were skin tested with intradermal liver extract before and after the institution of parenteral liver therapy, but the authors could find no correlation between the results of the skin tests and the presence or absence of eosinophilia following the use of liver extract parenterally. They state that it has not been demonstrated that the eosinophilia following liver therapy is allergic in nature, though they admit that this possibility has not been excluded.

It is apparent from an analysis of the available evidence presented so far that eosinophilia is very commonly found after the continued administration of either raw or partially cooked liver. With well-cooked liver and with oral liver extract eosinophilia only occasionally occurs, and when present the level is never high. Reported instances of eosinophilia following the parenteral administration of liver extract are uncommon. Neither Allin and Meyer<sup>2</sup> in 1940, nor Whitby and Britton<sup>36</sup> in 1942, could find any references in the literature to such cases. The only instances of which we have knowledge are those

cases reported by Heilmeyer<sup>14</sup> and by Allin and Meyer.<sup>2</sup> Inasmuch as so few reports have found their way into the medical literature despite the large amounts of liver extract which are being used parenterally in all parts of the world, it would seem that eosinophilia as a result of parenteral administration of liver extract is indeed uncommon.

We have recently had the opportunity to study a patient who developed a marked eosinophilia following the parenteral administration of crude liver extract. Because, to our knowledge, this case represents the most marked eosinophil response to parenteral liver extract which we have encountered in our review of the literature, we are reporting the case in detail.

**Case Report.** L. V., a white female, 45 years of age, entered the Graduate Hospital, under the care of Dr. Henry Tumen on October 29, 1943, complaining of a generalized papular eruption of 1½ year's duration and jaundice of 1 year's duration. Shortly after the onset of her jaundice the patient noticed that her urine was becoming dark and that her stools were becoming clay colored. There was no history of fever or abdominal pain. Questioning revealed numerous attacks of urticaria in childhood and adolescence, but there was no history of asthma or allergic rhinitis. She was studied in another city and an exploratory laparotomy was advised. At operation, in September 1943, no extrahepatic biliary tract disease was found; the liver was enlarged and its surface presented a number of tiny grayish-blue areas; the spleen was markedly enlarged and was removed. Following surgery the patient's jaundice and pruritic papular eruption persisted.

Examination on admission to the Graduate Hospital revealed a thin white female who was obviously jaundiced. There was no fever or adenopathy. Xanthomatous plaques were scattered over her entire body, being especially noticeable in the palms of the hands and in the region of the outer canthi of her eyes. The lungs were negative, and examination of the heart revealed an apical systolic murmur. Blood pressure was within normal limits. The liver was palpable 3 finger-breadths below the right costal margin and 4 finger-breadths below the xiphoid process in the epigastrium; it was firm and presented a finely nodular surface to palpation. Rectal examination was nonrevealing. No neurologic abnormalities were found.

During her hospital stay repeated urine analyses were negative except for the presence of bile and traces of albumin. The erythrocyte count varied from 3.1 to 4.7 million cells per c.mm., the hemoglobin ranging from 9 to 12 gm. %. Several platelet counts were within normal limits. Occasional target cells were found in the blood smears, but Howell-Jolly bodies were not seen. The total leukocyte and differential counts during the period of hospitalization are graphically presented in Figure 1. The blood sugar was 96 mg. per 100 cc., the alkaline phosphatase 11.8 Bodansky units, and the cholesterol 1608 mg. per 100 cc. The total serum proteins varied from 8.64 to 6.08 gm. % with an albumin component of from 4.85 to 3.45 gm. %. The prothrombin time on repeated occasions ran the gamut from 100% of normal to 27% of normal, and the serum bilirubin ranged from 30 to 4.5 mg. per 100 cc. The cephalin flocculation test was strongly positive.

The patient was placed on a high protein, high carbohydrate, and low fat diet with vitamin supplements, and parenteral glucose was administered daily. The hepatic status gradually improved so that when the patient finally left the hospital on February 16, 1944, the cholesterol had fallen to 594 mg. per 100 cc. with esters of 388; the serum bilirubin level had decreased to 0.8 mg. per 100 cc.; and the xanthomatous plaques, though still present, had largely receded. The diagnosis on discharge was non-obstructive biliary cirrhosis, unverified.

From November 27, 1943, until January 6, 1944, the patient was given a daily intramuscular injection of Lilly's crude liver extract. At no time during

the administration of the liver extract did urticaria, rhinitis, wheezing, or any other manifestations of an allergic nature appear. A blood count on January 5 revealed a leukocytosis of 19,850, with 11,286 eosinophils per c.mm. Because it was thought that this marked eosinophilia might be due to the administration of liver extract, the use of this substance was discontinued. During the succeeding 4 weeks the eosinophilia gradually decreased until on February 7 only 3% of the total leukocyte count of 9550 cells per c.mm. was of the eosinophilic series. That evening the patient was given 2 minims of the crude liver extract intradermally, but no wheal or erythema resulted, and that same evening a single dose of 2 cc. of the crude extract was administered intramuscularly. Fifteen hours later the eosinophils numbered 693 per c.mm., and on the following day there were 2882 eosinophils per c.mm. The changes in the total and differential leukocyte counts throughout the patient's hospital stay are graphically presented in Figure 1. At no time were young or immature cells of the eosinophil series present in the blood smears.

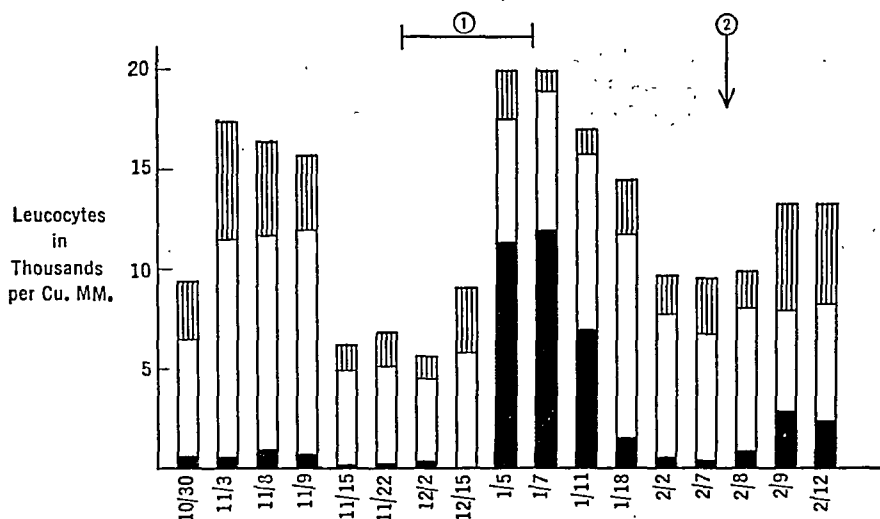


FIG. 1.—A graph of the patient's total leukocyte and differential counts. Solid areas, eosinophils; clear areas, neutrophils; striped areas, lymphocytes, basophils and monocytes. ① Lilly's Crude Liver Extract, 2 cc. I.M., daily from 11/27/43 to 1/6/44. ②, One dose of 2 cc. of Lilly's Crude Liver Extract I.M. on the evening of 2/7/44.

**Discussion.** The significance of and the mechanism underlying the development of eosinophilia following liver therapy are still matters of surmise. Watkins and Berglund<sup>34</sup> were of the opinion that eosinophilia might represent the reaction of the body to overdosage with liver, whereas Whitby<sup>35</sup> believed that the presence of eosinophilia was a favorable prognostic sign in patients undergoing treatment for pernicious anemia. Barone and Costa<sup>4</sup> observed that eosinophilia did not occur after the administration of raw stomach or stomach extract for pernicious anemia, and they ventured the opinion that the eosinophilia occurring as the result of liver therapy bears no relationship to the presence of the unidentified antipernicious anemia factor. Seyfarth<sup>31</sup> and Griva<sup>13</sup> considered the eosinophilia following liver therapy as an indication of bone marrow stimulation. Meulengracht and Holm<sup>25</sup> regarded it as a harmless phenomenon and felt that it bore no relation to the curative effect of liver in pernicious anemia. Massobrio and Maranzana<sup>23</sup> concluded from their observations that the substance in

liver responsible for the development of eosinophilia was thermolabile in nature, and the presence of eosinophilia in the new-born infant at a time when the mother's blood showed marked eosinophilia, in the case study reported by Corelli,<sup>6</sup> might indicate that the provocative substance may be able to pass through the placental barrier.

Although the mechanism underlying the eosinophil response to liver is not clear, an allergic mechanism has been hypothesized by many as an explanation of this phenomenon. It is of interest in this connection that in none of the reports of eosinophilia following the administration of liver or liver extract which we have reviewed was any mention made of concomitant findings suggestive of or indicative of a clinical allergic state such as asthma, urticaria, shock, etc. On the other hand, a number of reports have appeared in recent years concerning allergic manifestations which have occurred in the course of parenteral liver extract therapy,<sup>7,8,12,16,19</sup> the most recent review article on the subject being that of Kaufman and Farmer.<sup>17</sup> In only one report<sup>3</sup> was mention made of eosinophilia. Since allergic reactions to whole liver, either cooked or raw, or to liver extract by mouth are extremely uncommon as compared with the number of allergic reactions following parenteral liver therapy,<sup>17</sup> and since eosinophilia following whole liver by mouth is much more frequent and much more marked than with parenteral liver extract, it seems logical to us to conclude, as did Epler,<sup>10</sup> that eosinophilia following the administration of liver or liver extract is not related to the development of allergy in any of its known manifestations.

It is of interest that the eosinophilia in our present case report was not accompanied by any clinical manifestations of frank allergy and that the intradermal skin test with the liver extract used was negative. If allergy is to be implicated as the mechanism involved in the production of eosinophilia in this instance, it must necessarily be a monosymptomatic allergy characterized by eosinophilia alone. We have no basis upon which to postulate this.

What rôle the absence of a spleen in our patient may possibly have played in the development of eosinophilia following parenteral liver extract administration must remain a moot question. There is some evidence to show that there is a relationship between the spleen and the number of eosinophils in the circulating blood. Although Ishihari<sup>15</sup> was of the opinion that the spleen had no regulating influence on the eosinophil count in the guinea-pig, Mayr and Moncorps<sup>24</sup> were able to produce eosinophilia in guinea-pigs following splenectomy and were then able to reduce the number of eosinophils in the circulating blood by the injection of protein-free splenic extracts. Instances of eosinophilia following splenectomy in humans are cited by Downey,<sup>9</sup> and Kirk<sup>18</sup> has observed the development of eosinophilia in 5 of 8 patients who were subjected to splenectomy.\* He found that eosinophilia occurred as early as the 6th postoperative week and persisted for as long as 38 months. Waldbott<sup>33</sup> has postulated that hypofunction of the spleen results in eosinophilia, whereas hyperfunction of the spleen

\* A postsplenectomy eosinophilia (6 to 20%), after complete disappearance for several weeks beginning about the third postoperative week, was observed by us<sup>22a</sup> in normal dogs many years ago.—EDITOR.



gives rise to hypo-eosinophilia, and Whitby and Britton<sup>36</sup> state that some weeks after splenectomy the eosinophils may constitute about 10% of the total numbers of leukocytes. It is conceivable that in the case which we have reported the absence of a spleen may possibly have been a predisposing factor to the development of eosinophilia subsequent to the administration of liver extract parenterally.

Wintrobe<sup>37</sup> makes no mention in his text of liver disease as a cause of eosinophilia, and Lichtman<sup>22</sup> in discussing the changes in the leukocytes which occur in patients with liver disease does not point out any alterations in the eosinophil count. It is, therefore, very unlikely that the presence of severe hepatic damage in our patient had any relation to the eosinophilia which occurred.

**Summary.** 1. The literature on eosinophilia following liver therapy has been reviewed.

2. Although eosinophilia, often of marked degree, is very commonly found after raw or poorly cooked liver has been administered continually, it is an uncommon finding following the use of well-cooked liver, of oral liver extract, and of parenteral liver extract.

3. The possible rôle of allergy in the development of eosinophilia following liver and liver extract has been briefly discussed, and the relationship between the spleen and eosinophilia has been commented upon.

4. A case of marked eosinophilia following parenteral liver therapy has been presented.

We are indebted to Dr. Henry Tumen for permission to report this case and for his interest during the preparation of this manuscript.

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## THE PROGNOSTIC VALUE OF MARROW EOSINOPHILS IN THROMBOCYTOPENIC PURPURA\*

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THE value of marrow examination in thrombocytopenic purpura has become well established. By its means, thrombocytopenias have been classified into "secondary" and "primary" types. The former term encompasses a group characterized by the replacement of the marrow by various tissues, a replacement also involving the platelet parent cell—the megakaryocyte. The latter group, on the other hand, apparently has no gross morphologic basis, the megakaryocytes, in the greater number of instances, being present in abundance. It is in these cases that the spleen became incriminated and its "inhibitory" or "thrombolytic" activity made plausible by the dramatic results following its removal.

It was while studying a group of these "primary" thrombocytopenic purpuras that we became impressed by the close correlation between the clinical course and the number of eosinophils in the marrow. In a series of 30 cases here reported, it is shown that increased numbers of eosinophils in the marrow signify a favorable prognosis for spontaneous recovery, while scant numbers foretell a chronic course and the necessity for splenectomy. We believe that the marrow eosinophilia in these cases indicates an allergic state, and that the thrombocytopenia represents a "sensitization" reaction involving the megakaryocytes.

**Material and Methods.** The 30 cases studied were all typical thrombocytopenic purpuras characterized by marked reduction in the number of platelets, prolongation of the bleeding time, delayed clot retraction, abnormal bleeding from the body orifices, petechiæ and ecchymoses in the skin and mucous membranes, and decreased capillary resistance. The patients ranged in age from 2½ to 64 years. Their histories of purpura anteceded the observation period by from 1 day to 17 years. Marrow was obtained in each instance by aspiration biopsy from the sternum. Direct smear preparations were made and

\* Aided by a grant from the Wilson Laboratories, Chicago.

stained in the usual manner with Romanowsky stains. In determining the degree of the eosinophilia it was found that simple percentage figures were subject to considerable variations depending on *relative* increases in other cell types. Therefore, it was deemed advisable to compare the number of the eosinophils with cells of a like character. Since eosinophils presumably arise from the same stem as the neutrophils, and since in the majority of instances no specific stimulation of the granulocytes occurs in thrombocytopenic purpura, we selected these cells as a basis of comparison. Thus, neutrophilic granulocytes in an analogous state of maturation (*i. e.*, metamyelocytes or older) were used as a yardstick. No cells earlier than metamyelocytes were included in either the eosinophil or neutrophil counts, since it was felt that specific granulation in earlier cells might not be unequivocally identified. In each instance the number of eosinophils observed in counting 1000 granulocytes of the neutrophilic series was determined. From 2 to several thousand neutrophils were counted in each case, and rather close agreement was found for each group of 1000 cells done by different observers, suggesting that the counting of 1000 cells will usually suffice. With experience, the impression gained from merely "scanning" the smears will be found to correlate remarkably well with the actual counts, and we have learned to rely much on "impression" in the borderline cases.

TABLE 1.—THE NUMBER OF EOSINOPHILS IN THE BONE MARROW WITH THE PREPONDERANCE OF DEATHS AND CHRONIC PURPURAS IN CASES WITH LESS THAN 50 EOSINOPHILS PER 1000 GRANULOCYTES

Spontaneous recovery		Chronic purpura		Successful splenectomies		Deaths		Disappeared without recovery	
Eosinophils per 1000 marrow granulocytes		Eosinophils per 1000 marrow granulocytes		Eosinophils per 1000 marrow granulocytes		Eosinophils per 1000 marrow granulocytes		Eosinophils per 1000 marrow granulocytes	
Case No.		Case No.		Case No.		Case No.		Case No.	
<i>Few Eosinophils in Marrow</i>									
10	38	11	33	13	54, 36	23	26	26	23
		12	32	14	41	24	37		
				15	43, 35, 35	25	44		
				16	22	27	35		
				17	33				
				18	33				
<i>Many Eosinophils in Marrow</i>									
1	52			19	78				
2	63, 98, 83			20	59				
3	53			21	52, 53				
4	94			22	81				
5	136								
6	83								
7	76								
8	56								
9	50								
28	322								
29	73, 50								
30	133								

The eosinophil counts (per 1000 granulocytes) ranged from 22 to 322. The selection of 50 as the borderline figure was on the basis of experiment alone (Table 1), figures below this occurring in the non-recovery

series, and figures above this being found in those with spontaneous recoveries.

The cases studied fell into two major groups: those with low, and those with high marrow eosinophil counts. Those with low counts (14 cases): 1 recovered spontaneously; 1 disappeared from observation without recovery; 6 were successfully splenectomized; 4 died (1 before, 1 during and 2 after splenectomy), and 2 were chronic. Those with high marrow eosinophil counts (16 cases): 12 recovered spontaneously; 4 were successfully splenectomized; and none died.

**Analysis of Cases.** CASES 1 to 9 and 28 to 30. *Characterized by high number of eosinophils in the marrow and spontaneous recovery.* It is believed that these cases are secondary to sensitivity to foods, drugs, or microorganisms, and that when the offending agent is removed, recovery ensues. It is most likely that the thrombocytopenia is precipitated in "allergic" individuals by the action of a trigger mechanism, and that the clinical symptoms represent a "summation" effect. Only on this basis can it be explained that these episodes are unique and do not recur even though many of the offending agents continue to exist in the patient's milieu. It is our impression that transfusions of blood hasten recovery. In acute cases, where bleeding is extensive, transfusions act by partially replacing platelets. For this reason it has been our custom to employ fresh in preference to stored blood. It is interesting that Case 5 should have had so slow a recovery. Two explanations for this are offered: (1) he was given pectin derived from apples and oranges, two of the fruits to which he was found highly "skin sensitive"; and (2) he was not placed on an elimination diet for several weeks. It is recognized that skin sensitivities do not necessarily reflect marrow sensitivity, so that even though the patient may be found "skin sensitive" to something, he is not necessarily "marrow sensitive," and by the same token negative skin sensitivity does not preclude marrow sensitivity. Much work remains to be done on this subject before it can be removed from the realm of speculation. The significant conclusion to be drawn from this group is that it represents one in which complete recovery may be anticipated relatively shortly without the necessity of performing a splenectomy.

CASE 10. *Characterized by few eosinophils in the marrow and spontaneous recovery.* This case apparently belongs to the previously described group. We feel that failure to examine the marrow until the platelets had returned to normal accounts for the disappearance of the eosinophilia.

CASES 11 and 12. *Characterized by few eosinophils in the marrow and a chronic course.* These cases represent the non-allergic type of chronic cases which are candidates for surgery. Both are relatively benign, even though one has a 3 year and the other a 17 year history.

CASE 13. *Characterized by many eosinophils in the marrow and a chronic course.* The eosinophils in this patient's marrow were just over the arbitrary borderline on one occasion, but a repeat marrow examination 3 years later definitely placed him with the following group.

CASES 14 to 18. *Characterized by few eosinophils in the marrow, and responding to splenectomy.* In this group, cases varied from the fulminant course observed in Case 15, to the chronic and relatively benign course seen in Case 14. It is felt that these, together with the others characterized by low eosinophils, represent the so-called "essential," "primary," or "idiopathic" thrombocytopenias which, provided there is no dearth of megakaryocytes, respond well to splenectomy.

CASES 19 to 21. *Characterized by numerous eosinophils in the marrow, and responding well to splenectomy.* Each of these cases was observed over a relatively long period of time, but no attempts were made to determine either the effect of elimination diets or the possible causes of sensitivity, the cases antedating the recognition of the significance of marrow eosinophilia. These cases

TABLE 2.—SUMMARY OF OBSERVATIONS ON 30 CASES WITH THROMBOCYTOPENIC PURPURA

Case No.	Name	Age (yrs.)	Sex	Color	Length of illness when first seen	Suspected etiology	Course	Termination	Treatment	Eosinophils per 1000 marrow granulocytes	Remarks
1	K. F.	41	M	W	2 days	None	Acute	Rec. 13 days	Blood trans.	52	
2	S. C.	24	F	C	4 days	Drug given after tooth extraction	Acute	Rec. 9 days	Blood trans.	63, 98, 83	
3	G. Y.	6	F	W	3 days	Resp. infect.	Acute	Rec. 7 days	Blood trans.	53	
4	O. M.	64	F	W	8 days	Anacin	Acute	Rec. 13 days	...	94	
5	G. B.	5	M	W	13 days	Food and sulfonamide sensitivity	Subacute	Rec. 30 days	Blood trans.; elim. diet	136	Extensive allergic investigation; multiple food sensitivity
6	Z. G.	47	M	W	4 days	None	Acute	Rec. 12 days	Blood trans.	83	
7	B. L.	35	M	W	21 days	Food—molds; aspirin	Subacute	Rec.	Elim. diet	76	Extensive allergic investigation; multiple food and mold sensitivity
8	S. W.	12	F	C	1 day	None	Acute	Rec. 20 days	Blood trans.	56	
9	G. L.	42	F	W	10 days	Neocarsphenamine	Acute	Rec. 14 days	Blood trans.	50	
10	A. J.	16	M	C	5 days	Resp. infec.; aspirin; bromo-quinine	Acute	Rec. 19 days	Blood trans.	38*	Stormy course with severe epistaxes
11	F. A.	39	M	C	17 yrs.	None	Chronic	Unch.	...	33	
12	G. E.	9	F	W	4 wks.	None	Chronic	Impr.	Blood i.m.; snake venom	32	Platelets 105,000 3 yrs. later; no bleeding
13	G. J.	20	M	W	10 yrs.	None	Chronic	Unch.	...	54, 36	
14	B. L.	45	F	W	18 yrs.	None	Chronic	Rec.	Splenectomy	41	
15	Z. E.	13	F	W	5 days	None	Acute	Rec.	Splenectomy	43, 35, 35	

Case No.	Sex	Age	Color	Duration	Course	Diagnosis	Prognosis	Remarks
16	W.	57	F	3 yrs.	None	Chronic	Rec.	Splenectomy
17	J. M.	39	F	7 yrs.	None	Chronic	Rec.	Splenectomy
18	M. M.	30	F	6 mos.	None	Chronic	Rec.	Splenectomy
19	K. S.	20	M	1 yr.	None	Subacute	Rec.	Splenectomy
20	B. V.	11	F	7 mos.	None	Chronic	Rec.	Splenectomy
21	M. C.	20	F	1½ yrs.	None	Chronic	Rec.	Splenectomy
22	R. K.	16	F	1 mo.	None	Subacute	Rec.	Splenectomy
23	U. L.	17	M	16 days	None	Acute	Died	Splenectomy
24	B. S.	32	F	4 yrs.	None	Chronic	Died	Splenectomy
25	B. N.	22	F	8 mos.	None	Chronic	Died	Blood trans.
26	P. C.	6½	M	5 wks.	Sulfapyridine ?	Chronic	Impr.	Blood trans.
27	M. D.	40	F	1½ yrs.	None	Chronic	Died	Splenectomy
28	W. S.	9	M	4 wks.	Food	Subacute	Rec.	Elim. diet
29	R. J.	25	F	3-4 yrs.	Food	Chronic	Rec.	Elim. diet
30	L. T.	2½	M	5 days	Food	Subacute	Rec.	Elim. diet

\* Marrow obtained at time platelets were rising. 3 days before discharge from hospital.

† With acute exacerbation.

seem to indicate that even if the thrombopenia is on an allergic basis, the removal of the spleen can be beneficial. The mechanism of this action is unelucidated. Case 21 may not strictly belong to this group, resembling Case 13 in its closeness to borderline. It is possible, in view of the evidence here presented, that these cases may have been spared splenectomy by further studies.

*CASE 22. Characterized by increased numbers of eosinophils in the marrow, and responding to splenectomy.* This case should, strictly speaking, be classified as "secondary" thrombocytopenia, since the spleen itself was involved by Boeck's sarcoid. What effect this had on the marrow is conjectural. Whether the marrow eosinophilia represented a sensitization and a consequent thrombopenia similar to those of the other allergic types, or whether the eosinophilia was part of the underlying disease process and the thrombopenia secondary to the hyperactivity of the diseased spleen, cannot be deduced from the study of a single case, but we are inclined to the latter view.

*CASES 23 to 25 and 27. Characterized by few marrow eosinophils, and the death of the patients.* These cases varied from the acute, fulminant course seen in Case 23, to the chronic course of Case 24. These cases resemble Cases 13 to 18, which were also characterized by low eosinophil counts, but responded well to splenectomy. It is significant that the only 4 deaths in our series occurred in cases with few eosinophils in the marrow. It is felt, in retrospect, that had the significance of the low eosinophils been understood and these patients splenectomized without much procrastination, at least Cases 24 and 25 might have been saved.

*CASE 26. Characterized by paucity of eosinophils.* This patient was observed for about 2 months, during which period there was considerable clinical improvement, without the platelets ever rising over 65,000. At the time of this study, he could not be traced for follow-up purposes.

**Discussion.** Since Werlhof's description (1735)<sup>17</sup> of purpura, we have made steady progress in elucidating the nature and differential diagnosis of the disease. Donne (1842)<sup>4</sup> was supposed to have originally described platelets ("globulins") in the blood, while Denys (1887)<sup>3</sup> was the first to show that there was a reduction of the circulating platelets in Werlhof's purpura. This helped differentiate the vascular purpuras and scurvy from the thrombocytopenic forms. With the demonstration by Wright (1910)<sup>18</sup> that platelets arose from the megakaryocytes in the marrow, and the recognition that in spite of the blood thrombocytopenia the marrow megakaryocytes were present in normal or even increased numbers, either a megakaryocyte maturation defect (Frank, 1915)<sup>5</sup> or an increased platelet destruction (Kaznelson, 1916)<sup>7</sup> were suggested. Because of his belief in the destructive action of the spleen, Kaznelson was the first to have splenectomy performed in a case of thrombocytopenic purpura. The success of his case stimulated much interest, and within the next 20 years splenectomy became established as a curative procedure. As the number of cases increased, however, it became apparent that not all cases were cured by splenectomy. With the introduction of marrow biopsy by sternal puncture by Seyfarth (1923)<sup>14</sup> and its simplification by Arinkin (1929),<sup>1</sup> diagnosis could be made with more certainty since secondary purpuras could be ruled out.

In 1933 Denning<sup>2</sup> reported 3 cases of thrombocytopenic purpura following the administration of "Jotifixtabletten" (tablets containing 0.03% iodine), with 1 of the patients also developing thrombocytopenic purpura after Sedormid (allyl-isopropyl-acetyl-carbamide) ingestion.

Numerous reports confirming these findings have occurred since then, and other drugs (quinine, ergot, sulfonamides) have also been incriminated. In 1937 Squier and Madison<sup>15</sup> demonstrated that thrombocytopenic purpura could be produced by food allergy and cured by the removal of the offending agent. Thrombocytopenic purpura may also occur during or after infections, 12 of 153 cases being of this type in Rosenthal's<sup>13</sup> series.

Since presumably in allergic conditions the findings of an eosinophilia is common, and since the eosinophils have as their source the marrow, it might be expected that the marrow eosinophils be increased, even more markedly and more uniformly than those in the peripheral stream. Habelmann<sup>6</sup> has confirmed this by differential counts done on normal, moderately allergic, and severely allergic individuals.

To the present time the entire emphasis in marrow studies in thrombocytopenic purpura has been on the megakaryocytes. Limarzi and Schleicher<sup>9</sup> have summarized the present concept of the rôle of the megakaryocytes in thrombocytopenic purpura, emphasizing the inhibitory rather than the destructive effects of the spleen, a view with which we are not thoroughly in accord.

The eosinophils have been noted and commented upon in numerous publications dealing with thrombocytopenic purpura, but no previous correlation between their number and the clinical course has been made. Vogel, Erf and Rosenthal,<sup>16</sup> in commenting on the marrow findings in purpuras, note that "some of the cases showed a lymphocytosis and some of them had an eosinophilia. The cases of secondary purpura showed similar changes." Morrison and Samwick<sup>10</sup> note that "eosinophilia was also prominent in most of the cases. The latter was probably due to absorption of blood on the basis of foreign protein sensitization." Lawrence and Knutti<sup>8</sup> comment on the eosinophils in 5 of 6 of their cases. In 3 of them the eosinophils were increased, in 2 not increased. No attempt is made to draw conclusions or to correlate these findings.

When the correlation between high eosinophil counts and spontaneous remissions first became apparent to us, the findings were based on impressions only. In order to verify the impression we began determining eosinophil percentages, only to discover great discrepancies between what had appeared as obvious findings and actual counts. Interestingly, Nickerson and Sunderland<sup>11</sup> had apparently come to the same conclusion, for in their paper they state that "differential cell counts have shown no fundamental differences" between idiopathic thrombocytopenic purpuras, other purpuras, and normals. Reich and Kolb,<sup>12</sup> analyzing quantitative marrow studies statistically go so far as to state that "the validity of quantitative marrow determinations is very questionable."

Notwithstanding these objections, so obvious were the changes that we were convinced that some quantitative correlation could be established. It became obvious that one of the major causes of the great fluctuation in the percentage of eosinophils was the variability of the surrounding cell population. Thus, with bleeding there would be a



*relative* decrease in eosinophils due to increased erythropoiesis, while in children the greater number of lymphocytes tended to alter the percentage figures. Using comparative values rather than percentage figures (as discussed above), remarkably close correlation could be established between the height of the eosinophil level and the clinical course. Of the 30 cases studied, the correlation in 25 was perfect; 5 cases did not comply grossly. Of these, 1 had low eosinophils notwithstanding which he recovered spontaneously; 4 had to have their spleen removed, even though they had numerous eosinophils. Of these, 1 proved to be secondary thrombopenia on the basis of sarcoidosis of the spleen, while the other 3 may or may not have responded to conservative management, no allergic studies or treatment with this in mind being carried out. As was pointed out above, it is noteworthy that these cases recovered—even though their etiology may have been allergy—after removal of the spleen.

It is extremely significant that none of the 4 patients who died had an eosinophil count over 44, their counts being definitely below the arbitrary level. Attempts to correlate peripheral eosinophilia with marrow eosinophils or with clinical findings were unrewarded.

Multiple observations on the marrow were made in 5 cases. In Case 2 the eosinophils numbered 63 on admission, 98 two days later, and 83 four days after this. In Case 15 the eosinophils numbered 41 on admission, 35 three days later (the day of splenectomy), and 35 three days after this. In Case 13 the eosinophils numbered 54 on the first examination (slightly over borderline) but only 36 on repeat examination three years later. In Case 21 the eosinophils numbered 52 before and 53 one year after splenectomy. In Case 29 the eosinophils numbered 73 during the thrombocytopenic phase and 50 three months later when the patient had recovered. It would seem from these figures that the tendency for either a low or high eosinophil count is constant.

It is obvious that in dealing with marrow, which is influenced by so many variables and which reflects not only the stress and strain of the moment, but mirrors events both remote and recent, prognoses based on the numerical variation of a certain cell must be made with caution. It is our feeling, a feeling accentuated by the cases of exception, that the findings here reported do not represent either a fool-proof numerical prognostic system or a ready substitute for sound clinical judgment. Nonetheless, certain definite correlations are apparent, correlations which should add another tool to help make prognosis more certain and treatment more rational.

**Summary and Conclusions.** 1. Thirty cases of "primary" thrombocytopenic purpura are presented.

2. "Primary" thrombocytopenic purpuras may be divided into at last 2 types with respect to eosinophils: (a) with increased numbers of eosinophils in the marrow; (b) with no increase in marrow eosinophils.

3. Significant clinical, prognostic, and therapeutic differences are demonstrated between the two types.

4. It is suggested that the high eosinophilia is a manifestation of an

allergic state, of which the thrombopenia is merely another symptom, and therefore those cases having high eosinophil counts are thrombocytopenias *secondary* to sensitization, or "allergic" thrombopenias.

5. Cases characterized by high marrow eosinophils are thought to be due to sensitivity, are usually acute in onset and course, occasionally follow infections or the ingestion of drugs or allergenic foods, have relatively benign courses, and are followed by complete clinical and hematologic recovery.

6. In "allergic" thrombopenias, the elimination of the offending agent is curative; the removal of the spleen is *not* necessary; and blood transfusions seem to hasten recovery.

7. Thrombocytopenic purpuras with few eosinophils in the marrow remain in the "primary" group, and should have splenectomies.

8. No correlation was found between the eosinophils in the peripheral blood and the eosinophils in the marrow.

9. It is hoped that subsequent studies will further clarify the problem of "primary" thrombocytopenic purpuras and ultimately enable us to dispense with the term altogether in favor of etiologic diagnoses.

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## INFECTIOUS MONONUCLEOSIS AND THE NEGRO

### WITH A REPORT OF 6 CASES

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INFECTIOUS mononucleosis as a disease entity has been known for over 50 years. The first record is that of Filatow<sup>6</sup> of Moscow, who de-

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scribed cases of acute enlargement of the cervical lymph glands without associated inflammatory changes in the mouth, nose or pharynx. Emil Pfeiffer<sup>17</sup> in 1889 gave an excellent description of the disease which he called "Drusenfieber" (glandular fever). In 1896, glandular fever first appeared in the American literature when West<sup>20</sup> described a comparatively large epidemic in eastern Ohio. The term "infectious mononucleosis" was introduced in 1920 by Sprunt and Evans,<sup>19</sup> who first emphasized the blood cytology. It was not until 1922 (37 years after the disease was first recognized) that the first case occurring in a Negro was reported by Longcope.<sup>13</sup> This patient was a boy who had an acute febrile disease with enlargement of the lymph nodes, spleen and liver. He also had a marked mononucleosis.

In 1940, Bernstein<sup>2</sup> published his excellent study of the disease based on a series of 65 patients at the Johns Hopkins Hospital. Not one of these was a Negro. He says in discussing these cases: "Sporadic cases, unless studied by the aid of repeated differential blood counts, may readily be overlooked while medical students or nurses, promptly admitted to the hospital for treatment of even a trifling illness, are almost certain to be correctly diagnosed by the routine methods of examination. This explanation, too, may account for the apparent paucity of cases observed in the dispensary and public wards as well as the rarity of infectious mononucleosis among Negroes, of whom not a single one appeared in our cases.<sup>13</sup> Indeed, but a single instance in a Negro has been noted in the literature." Wintrobe<sup>21</sup> in 1942 reiterates that the disease in the Negro is limited to 1 reported case (that of Longcope).

In April 1944, 22 years after the publication of Longcope's case, Johnson<sup>9</sup> reported 2 cases occurring in Negro children at the New Haven Hospital. These 2 cases are the first serologically proven cases in the Negro to be published. The first had a heterophil agglutination titer of 1:640. After adsorption with guinea-pig kidney the titer was 1:320. The second had a titer of 1:2560. Johnson states that "no explanation can be offered for the apparent rarity of the disease on a racial basis."

*Anthropologic Considerations.* Infectious mononucleosis occurs in many racial and ethnic types and it has been reported in many widespread areas throughout the world. America, Australia, France, Germany, Russia, and Great Britain have all had epidemic and sporadic cases. Benson<sup>1</sup> has written of the disease in Scotland. It has been seen in South America<sup>8</sup> and the Philippines. It was reported in Hong Kong in 1897.<sup>3</sup> Priest<sup>18</sup> has recognized it in Egypt. Infectious mononucleosis has been encountered in Trinidad<sup>4</sup> and in the Falkland Islands.<sup>15</sup> In Japan, the following epidemic fevers have been shown by the use of Paul-Bunnell tests to be identical with infectious mononucleosis:<sup>11</sup> tosa-netsu, tokushima-netsu and kagami-netsu. Bernstein is of the opinion that the disease has no racial preference. He mentions the epidemic followed at the London Hospital and reported by Gooding,<sup>7</sup> in which "20 of 27 cases occurred among Jews, a fact perhaps ascribable to the area served by the hospital."

Thus, it may be seen that, so far as is known, the occurrence of infectious mononucleosis does not appear to be limited by factors of geography or race; indeed, it is world-wide in its distribution, affecting many ethnologic varieties of man.

Furthermore, it can be seen why sporadic cases in the Negro would not come to the attention of physicians as readily as similar cases in others, especially in college infirmaries and elsewhere where either white patients predominate or have access to better diagnostic facilities.

There is then no known reason why the disease should not afflict Negroes as commonly, relatively, as the members of other races, and it does so in our series of cases.

**Clinical Study.** The occurrence of this disease in 6 Negroes in our series of 20 sporadic cases at the Receiving Hospital from 1934 to 1944 indicates that the disease is not as rare in the Negro as has been heretofore supposed. The case reports to be presented represent 30% of our total cases in a hospital where only 25% (as determined by spot samplings of several recent years) of the population is composed of Negroes.

The first 4 cases had heterophil agglutination titers of 1:224 or above. The fifth had a titer of 1:160 which is accepted as positive by Bernstein and others. The last case was seronegative although his titer could be classed as "borderline" as defined by Davidsohn<sup>5</sup> (*i. e.*, 1:56 to 1:112). He had, however, positive clinical and hematologic evidence for the diagnosis. In addition, 2 patients, each with a titer of 1:112, are mentioned.

**Case Reports.** CASE 1. F. M., an 18 year old Negro male, was admitted on August 8, 1941, complaining of a severe sore throat, malaise, and fever of 1 week's duration. On the first day of his illness his eyelids were swollen. On the day prior to admission the patient experienced a chill. There was no cough. The past history included attacks of mumps, pertussis, measles and chickenpox. At the age of 9 a tonsillectomy and adenoidectomy was done. Physical examination revealed a well-developed and well-nourished male who appeared acutely ill. Temperature 104.2°, pulse 82, respiration 20. The oral and nasal mucosa, the soft palate and uvula were markedly edematous and injected. There was a thick, greenish, purulent postnasal discharge. There were bilateral tender enlarged anterior and posterior cervical, submental, submaxillary and pre-auricular glands. The inguinal glands were small and shotty. On August 11, the spleen was palpated 2 fingerbreadths below the left costal margin.

**Laboratory Data.** Roentgen rays of the sinuses showed a slight cloudiness of the ethmoids and frontal sinuses. The urine was negative. A Kline test was negative and throat cultures were negative for diphtheria. Examination of the blood revealed a leukocytosis of 18,400 with 67% lymphocytes. The hemoglobin was 13 gm.

On August 13 the following blood study was made (E. C. V.): Red cells 5,120,000, reticulocytes 0.4%, hemoglobin 87%, thrombocytes 123,000, white cells 15,500 (neutrophils [stab] 12% and [segmented] 15%, lymphocytes 67%, monocytes 6%). There were many bizarre large lymphoid cells like those seen in infectious mononucleosis.

The heterophil agglutination on August 14 (2 weeks after onset of illness) was positive through dilutions of 1:1026. The patient was given sulfathiazol and local therapy and was discharged on August 15, after the temperature had been normal for 3 days.

CASE 2. M. G., a 13 year old Negro girl, was admitted to the Receiving Hospital on Sept. 25, 1943, complaining of a sore throat of 24 hours duration. She had had frequent sore throats and colds during the past 12 months. Physical examination revealed a well-developed and well-nourished girl in no acute distress. Temperature 102.8°, pulse 110, respiration 20. The nasal turbinates were swollen and injected as were the tonsils. Both the anterior and posterior cervical nodes were enlarged and tender. There were shotty inguinal nodes and palpable nodes in the left axilla. The liver and spleen were not palpable. The admission diagnosis was acute tonsillitis.

*Laboratory Data.* The urine was negative on several examinations. Nose and throat cultures were negative for diphtheria. The Kahn test was negative. Blood studies revealed: hemoglobin 10.5 gm., leukocytes 19,500 (of which 36% were "abnormal and toxic" lymphocytes, neutrophils 51% (35% were filamented and of the non-filamented forms—5 myelocytes, 5 stab cells and 6 juvenile forms). There were 5 monocytes, 2 blast cells, 2 basophils and 4 eosinophils, and the smears were reported as "suggestive of infectious mononucleosis." The heterophil agglutination was positive on September 29 (6 days after onset of symptoms) in a titer of 1:3594. This is the highest titer ever observed at this hospital. On September 30 the leukocyte count was 11,900, band form neutrophils 9%, polymorphonuclear neutrophils 20%, atypical lymphocytes 22%, eosinophils 1%, monocytes 3%. "The erythrocytes appear normocytic and normochromic. The majority of the atypical lymphocytes are reticular (Type 1 of Downey). Impression: infectious mononucleosis." (Dr. Lawrence Berman, Hematology Laboratory.)

On October 1 a tonsillectomy and adenoidectomy was done and the patient was discharged on the next day. She received sulfathiazol while in the hospital.

CASE 3. M. P., a 27 year old married female Negro, was admitted on Nov. 27, 1943, with a diagnosis of possible acute appendicitis. Her past history revealed that she had had a course of sterile milk shots at the Gynecologic Clinic of this hospital 1 year previously for chronic pelvic inflammatory disease. She had been married 5 years during which time she had been troubled by a chronic vaginal discharge. She had had 3 spontaneous miscarriages, the last occurring 4 months prior to admission. Two to 3 weeks before coming to the hospital she had a "head cold" associated with chills, sweating, cough, chest pain and a small amount of blood-streaked sputum. One week prior to admission she noted a mid-abdominal pain of sudden onset associated with nausea, vomiting and constipation. Physical examination revealed a well-developed and well-nourished, but markedly dehydrated woman in moderate distress. Temperature 99, pulse 70, respiration 22. The throat was injected, the tonsils had been removed, and a bleeding point was noted in the right nostril. No lymphadenopathy was noted. The spleen was not palpable but the liver was palpable below the right costal margin. The liver was tender and the abdominal tenderness was mainly in the right upper quadrant. There was bilateral costovertebral angle tenderness and there was a dermatitis later diagnosed as of contact etiology. The pelvic examination was deferred because she was menstruating but when done revealed an acute exacerbation of her pelvic inflammatory disease.

*Laboratory Data on Admission.* There was a leukocytosis of 14,850 (monocytes 20%, neutrophils 66%, lymphocytes 13%). A recheck the same day showed leukocytes 13,100 (monocytes 14%, neutrophils 76%, lymphocytes 8%). It is very likely that the monocytes were in reality atypical lymphocytes. There was no anemia or jaundice. The bleeding time was 1 minute 45 seconds and the clotting time was 2 minutes. The Kline test was negative, the blood urea was 153 mg. The urine contained 100 white cells, 1+ albumin and trichomonads. The albumin-globulin ratio was normal. Urine cultures were positive for *Staphylococcus albus*, *B. coli* and, later, a non-hemolytic streptococcus. By December 6 the blood urea had fallen to normal levels where it remained.

On December 7 the submandibular and submaxillary glands were enlarged

and tender. The liver was still palpable but the spleen was not. The following day (24 to 31 days after onset of symptoms) the heterophil agglutination was positive in dilutions through 1:224. Chest Roentgen rays, retrograde and intravenous pyelography and urea clearance tests all yielded normal results. The blood picture on December 6 was as follows: leukocytes 11,100, neutrophils 63% (filamented 60%, non-filamented 3%), lymphocytes 20%, monocytes 13%, 1 plasma cell, 1 basophil and 20% eosinophils.

The patient was treated with sulfathiazol, vitamins and sedation. Fluids were forced. Her temperature ran a septic course until December 14 (3 weeks after admission). At this time her liver was no longer palpable and her symptoms had disappeared. Final diagnosis: acute exacerbation of chronic pelvic inflammatory disease, bilateral acute pyelonephritis and infectious mononucleosis.

This case reemphasizes the fact that infectious mononucleosis is not only very protean in its manifestations but may well be associated with or obscured by coexisting disease.

CASE 4. M. M., a 27 year old Negro female, was admitted to the hospital on Jan. 7, 1944. She had been well until the 1st week in November 1943, since which time she had suffered from "a chronic cold" associated with a non-productive cough. One week prior to admission she developed a productive cough and a pain in the left lower costal region, anteriorly, for which she was given a sulfonamide drug by her family physician. Two days prior to admission she had blood-streaked sputum, fever, nausea and vomiting.

The physical examination on admission was essentially negative except for tenderness at the left costal margin anteriorly. There was no lymphadenopathy or splenomegaly. Temperature 98, pulse 110, respiration 24.

*Laboratory Data.* Roentgen rays were negative for rib fracture and showed slight exaggeration of the bronchovascular markings throughout both lung fields. It was the impression of the radiologist that these findings were consistent with "influenza with left pleuritis or recurrent bronchitis." The urine was negative. The white count was 9500 (lymphocytes 54%, neutrophils 42%, 2 monocytes and 2 eosinophils). The Kahn and a blood culture were negative. On January 11 the urine contained 5 to 10 white cells and a urine culture was positive for non-hemolytic streptococcus, *Staphylococcus albus* and diphtheroids. The following day the white count was 5850 (lymphocytes 46%, neutrophils 49%, monocytes 3%, 1 basophil and 1 eosinophil).

On January 14 (2 weeks after onset of acute symptoms) the heterophil agglutination was positive through a dilution of 1:224. The patient remained in the hospital for 1 week and was symptomless after the 2nd day except for tenderness along the left costal margin and over the spleen which was never palpable. No lymphadenopathy was ever noted in this case.

CASE 5. D. D., a 6 year old Negro boy, was admitted on Feb. 21, 1942, with a diagnosis of acute tonsillitis and possible blood dyscrasia. He had had a sore throat and a fever for several days with swelling of the glands of the neck. He had had a tooth extracted 4 days prior to admission and had bled for 2 days thereafter. He had a nosebleed on the morning of admission. He had been immunized against diphtheria and had had pertussis and measles. Physical examination revealed a well-developed and well-nourished but acutely ill boy. Temperature 103.2°, pulse 140, respiration 20. The tonsils were enlarged and inflamed with follicular surfaces. There were large tender submaxillary glands on the right and smaller ones on the left side. There was bilateral tender shotty cervical adenopathy. The spleen and liver were not palpable.

*Laboratory Data.* The urine was negative. Nose and throat cultures were negative for diphtheria. Examination of the blood revealed a leukocytosis of 12,550 (neutrophils 78%, lymphocytes 22%). The hemoglobin was 8 gm., the red cells 3,420,000.

He was placed immediately on sulfathiazol, cod-liver oil, orange juice and

iron. An ice collar was employed for local relief. The following day his temperature had dropped almost to normal and thereafter ranged between 98° and 99.5° until March 1 when it spiked to 101° (the sulfathiazol was discontinued on February 27). On March 5 the spleen became palpable 2 cm. below the costal margin. On this day the patient was started on sulfadiazine and the temperature returned to normal where it remained. The heterophil agglutination on March 10 was positive in dilutions through 1:128 and on March 19 through a dilution of 1:160 (over 1 month after onset of symptoms). The Kahn test, tuberculin test and chest Roentgen rays were negative as was a wet preparation of blood for sickle cells. The blood examinations are charted below:

Date	Hb.	R.B.C.	W.B.C.	Neut.	Lympho.	Eosin.
2/22/42 . . . .	8 0	3,420,000	12,550	78	22	
2/27/42 . . . .	8.5	3,340,000	9,900	87	13	
3/9/42 . . . .	9 0	4,450,000	9,700	48	52	
3/14/42 . . . .	9.0	..	11,300	62	35	3

By March 19 all the enlarged lymph nodes had decreased in size and the spleen was no longer palpable. On March 24 the patient was discharged.

It will be noted that although this patient's heterophil agglutination titer was only 1:160, he had lymphadenopathy, an enlarged spleen, sore throat and, at one time, a lymphocytosis.

Case 6 was interesting not only in that he was a Negro but also seronegative and his infectious mononucleosis was associated with acute thrombocytopenic purpura. This complication is exceedingly rare, there being only a very few unimpeachable cases in the literature. Magner and Brooks,<sup>14</sup> and Lloyd<sup>12</sup> have each reported a case in which first of all the diagnosis of infectious mononucleosis was unequivocal (their patients having positive Paul-Bunnell tests, lymphocytosis, typical blood cytology and lymphadenopathy, and the former splenomegaly as well). In addition, both cases had bleeding, purpuric eruptions, prolonged bleeding times, and reductions in platelet counts. Lloyd's case had a sternal puncture which showed no abnormality of the various bone marrow elements. Sternal puncture in our case also showed no abnormality.

Hemorrhagic skin eruptions, epistaxis, hematuria or bleeding from other mucous membranes (as in Case 5) in the presence of a normal platelet count is not uncommon in infectious mononucleosis and is probably due to capillary damage. ©

CASE 6. J. H., a 13 year old Negro boy, was admitted to the Nose and Throat service on Sept. 15, 1940, complaining of a severe sore throat of 3 days duration. He had such marked cervical lymphadenopathy that his whole neck appeared to be swollen. His past history was negative except for an attack of mumps. He was in good health until September 8, at which time he became conscious while sitting in a theater that his neck glands were enlarged. There was associated pain and swelling of the eyelids and a mild headache. Four days later the adenopathy and other symptoms subsided and he felt improved. On September 15 the swelling in the cervical nodes returned and he entered the hospital.

Physical examination showed a well-developed and well-nourished youth appearing acutely ill. Temperature 103°, pulse 80, respiration 18. The tonsils were hypertrophied but not injected. There were several petechiae on the soft palate. The anterior cervical, submaxillary and submental lymph nodes were enlarged, tender and firm to palpation and seemed to be matted.

The axillary glands were enlarged and tender. The spleen was palpable 2 fingerbreadths below the costal margin.

The impression was that he had infectious mononucleosis and he was transferred to the medical service as soon as the following blood study was reported: Hb 12.5%, white cells 20,000 (lymphocytes 80%, monocytes 5%), neutrophils 15%. The urine was negative. A Kahn test was negative and throat and nose cultures were negative for diphtheria. On the following day a complete blood study was made by one of us (E. C. V.) and is recorded below:

Hb . . . . .	84%
R.B.C. . . . .	4,180,000
W.B.C.* . . . . .	23,000
Reticulocytes . . . . .	1.5%
Platelets . . . . .	204,000

\* 5% stab forms, 3% segmented, 1% eosinophil, 1% basophil, 84% lymphocytes, 6% monocytes.

"Slight normochromic anemia. Leukocytosis with neutropenia and an absolute and relative lymphocytosis. Lymphocytes are the type seen in benign infectious mononucleosis. Impression: infectious mononucleosis."

The patient was treated with sedation and an ice collar for local relief. On September 25 the heterophil agglutination was positive through a titer of 1:64 (over 2 weeks after onset of symptoms). On this day the patient developed a severe nosebleed and had a prolonged prothrombin time (17 seconds, the normal being 12 seconds by Quick's method). He developed purpuric spots on both thighs and on October 1 the Rump-Leede test was markedly positive. It remained so for some time. Following the epistaxis the platelets fell to 20,000. A diagnosis of acute thrombocytopenic purpura was made. The bone marrow on study (E. C. V.) had a normal appearance with many normal megakaryocytes present. The prothrombin time remained elevated and the platelet count remained depressed until after discharge. On October 2 the Paul-Bunnell test was positive in dilutions through 1:16 only. On October 21 the hemoglobin was 81% and red blood cells 4,400,000. The white blood count was 7400 (lymphocytes 51%, neutrophils 39% [28% filamented and 10 non-filamented, 1 juvenile]). The platelets were 36,000. On October 22 a bromsulphonphthalein test showed no retention of dye at the end of 30 or 60 minutes. The patient was discharged on October 23. The final diagnosis was infectious mononucleosis and acute thrombocytopenic purpura.

Although we regard a titer of 1:64 as negative, we feel that the diagnosis is well established on clinical and hematologic evidence. It might be well to point out that well-substantiated seronegative cases such as that of Pearman and Brumm<sup>16</sup> do occur. They state in their report that "at present there is a certain number of seronegative cases in almost every large series reported, chiefly in sporadic cases among children." Their patient had a titer of 1:10. Also, there are 5 seronegative cases in Bernstein's series of 65. Bernstein states that "if the clinical picture is sufficiently characteristic therefore, a negative Paul-Bunnell test does not preclude the diagnosis of infectious mononucleosis any more than a negative Wassermann reaction rules out syphilis."

In addition there have been 2 Negroes who developed titers of 1:110 while in the hospital. Both had generalized lymphadenopathy. Neither had a palpable spleen. One had lymphocytosis. The first, a 21 year old woman, had given birth to her third baby 2 weeks prior to admission. She had a may, a pyelonephritis and a septic fever. The second,



a 17 year old boy, was markedly jaundiced; he had an acute hepatitis with a persistently positive serology. Both probably had infectious mononucleosis.<sup>10</sup> Unfortunately, neither had differential absorption tests or complete hemograms so the diagnosis could not be positive. None of the cases reported here gave any history of having received serum.

Since this article was submitted for publication Ray and Cecil<sup>18a</sup> have reported 3 serologically proved cases of infectious mononucleosis in negroes at the Medical College of Virginia Hospitals. One of these cases was complicated by sickle cell anemia. They also point out that 4 of the 21 cases reported by Werlin, Dolgopel and Stern from the Willard Parker Hospital in 1941 were negroes. Only one was given in detail, and in this the heterophil antibody titer was positive 1:112 (after absorption, 1:56). On admission the white count was 27,800 with 57% lymphocytes. On the 8th day there were 17,000 white cells with 54% lymphocytes of which 13% were abnormal. These 7 cases bring the correct total of reported cases in the Negro to 16.

**Summary.** Infectious mononucleosis although recognized as a disease entity for over 50 years has been reported in only 3 Negroes. Two of these, having been reported subsequent to the development of the Paul-Bunnell test (1932), are confirmed serologically.

The 6 cases reported here represent 30% of a series of 20 cases which have been diagnosed at the Receiving Hospital during the past 10 years. The proportion of Negro patients in this hospital is 25%. Inasmuch as these cases were all sporadic rather than epidemic there is an indication that the disease is as common as in the whites at this hospital.

Two of the cases had heterophil agglutination titers over 1:1000; 2 of the cases were positive in titers through 1:224; 1 was positive in titers through 1:160; and 1 was seronegative (1:64). This last case had excellent clinical and hematologic evidence for the diagnosis. He also had a rare complication, acute thrombocytopenic purpura. Two other probable cases of infectious mononucleosis are mentioned.

**Conclusions.** 1. Six cases of infectious mononucleosis in Negroes are reported. Five of these are serologically confirmed. One case was seronegative.

2. The seronegative case had an associated acute thrombocytopenic purpura, which is a rare complication. The 2 best substantiated cases of this complication reported in the literature are cited.

3. In addition 2 probable cases are mentioned but are not included in the series.

4. These cases bring the total of reported cases in Negroes to 9 and the total of serologically, proved cases to 7.

5. Infectious mononucleosis at this hospital is relatively as common in the Negro as in the white.

6. The widespread belief that infectious mononucleosis is rare in the Negro appears to be no longer tenable.

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## SPONTANEOUS PNEUMOTHORAX AS A COMPLICATION OF PNEUMONIA IN ADULTS\*

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PULMONARY tuberculosis is commonly thought to stand first as an exciting cause of spontaneous pneumothorax. It has been variously estimated that tuberculosis accounts for from 70%<sup>6</sup> to "at least" 80 or 90%<sup>14</sup> of all cases. The less common causes of spontaneous pneumothorax are abscess or gangrene of the lung, bronchiectasis, septic infarct, rupture of an emphysematous vesicle, rupture of a cyst in a congenital cystic lung and gas-producing organisms in a pleural effusion. It is also known to occur in healthy individuals without any clinically demonstrable evidence of pulmonary disease. In the group of extrapulmonary causes are perforation of the esophagus, rupture of a gastric ulcer or carcinoma through the diaphragm, and rupture of a liver abscess.

From the perusal of literature and text-books on general medicine, it appears that spontaneous pneumothorax as a complication of lobar or bronchopneumonia has escaped general recognition and has not come to constitute a part of common knowledge. While not an unusual complication of pneumonia in children,<sup>4,7</sup> it is still considered

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as an unusual occurrence in the course of pneumonia in adults. According to Lord<sup>12</sup> "Pneumonia is to be regarded as a cause only, insofar as it leads to conditions to which pneumothorax may be secondary." Of these conditions, perforation of empyema into the lung or rupture of an area of pulmonary abscess or gangrene into the pleura are mentioned. In Tice's "Practice of Medicine"<sup>16</sup> pneumothorax in association with pneumonia is considered to be "a very rare occurrence and has been noted most often when empyema has ruptured into a bronchus." In other words then, not pneumonia *per se*, but rather such pathologic processes as abscess, gangrene or empyema are credited with production of spontaneous pneumothorax. However, there have been reported in literature a few cases of pneumothorax in association with pneumonia not complicated by any of the sequelæ above mentioned. To these I add 2 more cases recently observed. Although there have been very few such cases reported, and in spite of statements made by some<sup>8</sup> that "the association of pneumothorax with pneumonia is extremely rare," it would appear that this condition is more frequent than has heretofore been thought.

*Review of Literature.* The earliest reference in literature to occurrence of spontaneous pneumothorax in association with pneumonia that I have been able to find is a report by Von Mering,<sup>18</sup> who in 1886 recorded 2 such occurrences in a review of 422 cases of pneumonia, an incidence of 0.47%. The diagnosis had apparently been made on the basis of physical findings only. The next report is by Aldridge and Mooring<sup>1</sup> who in 1915 described a case of pneumothorax following pneumonia in a bricklayer, age 40. The patient made an otherwise uneventful recovery. The same authors quote a personal communication from Dr. Arthur Latham as follows: "Some few years ago the pneumonia cases at the London General Hospital were analyzed for a period of 10 years in the Medical Section of the Royal Society of Medicine. As far as I know, in over 7000 cases there were not more than 3 complicated by pneumothorax, and 2 of them proved fatal."

During the influenza epidemic of 1918-1919, Berkley and Coffen<sup>5</sup> reviewed 1701 cases of bronchopneumonia, in which series 9 cases developed extensive subcutaneous and interstitial emphysema. Of these 9 cases, 2 had an associated spontaneous pneumothorax. The authors stated that it has been impossible to establish any relationship between the casual organism in a case of pneumonia and development of emphysema or pneumothorax. The organisms found were pneumococcus, non-hemolytic streptococcus, and *H. influenzae*. However, in 1 of these 2 cases with spontaneous pneumothorax, in addition to Type IV pneumococcus, acid-fast organisms were also discovered in the sputum. A tuberculous origin of spontaneous pneumothorax thus remains in question in this particular patient. It was thought that violent coughing served as an inciting factor, leading to the rupture of the lung. The report of Berkley and Coffen apparently served as a basis for the statement to be encountered in Tice's "Practice of Medicine"<sup>16</sup> to the effect that in the bronchopneumonia during the influenza epidemic of 1918-1919, coughing in some cases was so severe

"that it led to rupture of the lung. In four-fifths of these cases, however, it led to interstitial and, therefore, often to subcutaneous emphysema; only in one-fifth of them did pneumothorax develop."

Bassel,<sup>3</sup> reviewing 23 consecutive cases of spontaneous pneumothorax, refers to 3 found to be the result of pneumonia. Glickman and Schlomovitz<sup>10</sup> cite 2 cases of spontaneous pneumothorax following bronchopneumonia out of 82 cases of spontaneous pneumothorax following different conditions, an incidence of 2.5%. However, direct reference to the source<sup>9</sup> quoted by these authors surprisingly fails to reveal such actual occurrence. Therefore, these 2 cases have to be discounted.

Minet and Houcke<sup>13</sup> encountered 2 cases of pneumonia, 1 pneumococcal, complicated by small pneumothorax. Both patients recovered. Another case with bronchopneumonia complicated by pneumothorax with serous effusion died. At autopsy there was no evidence of acid-fast infection.

Aubertin, Lereboullet and Pergola<sup>2</sup> reported 2 cases. One with pneumonia was complicated by a pneumothorax which evolved into a pyopneumothorax with death of the patient. On autopsy a purulent effusion in the left pleural cavity, consolidation of the left base with diffuse changes of bronchopneumonia in the rest of the lung and a small cortical abscess posteriorly "without any apparent rupture into the pleura" were found. There were no acid-fast organisms found. In another patient pneumothorax was not accompanied by effusion and he successfully recovered.

Thomas<sup>17</sup> reported 7 cases of pneumonia complicated by pneumothorax. The recovered organisms were pneumococcus and non-hemolytic streptococcus. In 1 patient there was an associated serous effusion, in 2 empyema, and in the remaining 4 only pneumothorax. In 1 case initially a serous effusion later became purulent. In another case there developed an abscess of the chest wall. All 7 patients recovered.

Hyde and Hyde<sup>11</sup> found "a small apical spontaneous pneumothorax on the affected side" as a complication in 2 out of a series of 51 cases of primary Friedländer pneumonia.

**Report of Cases.** CASE 1. F. S., a 43 year old man, was admitted to the hospital on May 7, 1943, with complaints of chest pain, fever and cough of 3 days duration. He had been in excellent health in the past. On entry he was seen to be well developed and well nourished and appeared to be acutely ill, with rapid respirations and a pulse of 108. There were signs of consolidation of the right lower lobe confirmed by Roentgen ray studies. There were no other remarkable physical findings. There was a leukocytosis of 15,200. Pneumococci, Type VII, were found in the sputum. The response to therapy with sulfonamides was satisfactory, and the recovery was clinically uneventful. However, a routine check Roentgen ray film of the chest taken on May 14 revealed the presence of a small apical pneumothorax. Repeated examinations of concentrated sputum specimens failed to reveal any acid-fast organisms. No tubercle bacilli were found on cultures and the guinea-pig inoculation with the specimen of sputum also failed to show a tuberculous infection. On resorption of pneumothorax, there were no demonstrable lesions in the lung fields by Roentgen ray.

CASE 2. R. L., a 49 year old white male, was first admitted to the hospital in November 1938 for treatment of traumatic compression fracture of the

first and second lumbar vertebræ. The second admission was on Dec. 22, 1943, at which time he complained of fever, cough and weakness with breathlessness of 1 week's duration. The night before entry into the hospital he was seen by the family physician who made a diagnosis of pneumonia and recommended hospitalization. He had the usual childhood diseases but no other illness. He had been in good health all his life.

On physical examination the patient was seen to be a well-developed, fairly well-nourished man of about the stated age, acutely ill, cyanotic, with rapid and shallow respirations and a rapid, feeble, irregular pulse, 120. The temperature was 102° F. The blood pressure was 110/60. The examination of the heart did not reveal any significant findings, except for rather frequent premature beats. There was impairment of resonance on percussion with râles over the entire lung field on the right. There were no other significant findings.



FIG. 1.—Case 2. Diffuse opacity in right lung.

The urinalysis revealed the presence of 2+ albumin and some hyaline casts with a few granular casts. Red blood count was 3.7 million per c.mm.; hemoglobin, 9.5 gm. Total leukocyte count was 7200 (89 % neutrophils). Serologic blood tests were negative. Neufeld typing tests for pneumococci in the sputum (Types 1 to 33 inclusive) gave negative results. Roentgen ray film of the chest taken bedside revealed diffuse opacity in the right lung field (Fig. 1). Blood culture taken on admission failed to show any bacterial growth.

Within 1 hour after entry the patient became semistuporous. Because of the critical condition of the patient, sulfadiazine was administered intravenously, 4.5 gm. of the sodium salt as a 5% solution in sterile water. It was thought that frequent extrasystoles could be interpreted as indicative of an underlying organic heart disease with the heart laboring under the stress of an overwhelming infection. At any rate, digitalization was considered advisable. Six cc. of cedilanide (3 mg.) were given intravenously in addition to sulfadiazine and the patient was put into an oxygen tent. The following morning he seemed to have improved; he was conscious, well oriented, but still toxic. Blood sulfadiazine concentration of 12.6 mg. per 100 cc. of the free drug was reported. The patient was started on sulfadiazine orally, 1 gm. every 4 hours, and was also given another 2 cc. of cedilanide intravenously followed by cedilanide by mouth, 1 tablet 3 times a day. The following (2nd) day extrasystoles were no

longer present. On the 5th hospital day the temperature gradually dropped to 99° F. and the patient's condition seemed to be satisfactory.

However, this improvement was not lasting, as the temperature began to rise again in a few days and reached 103.6° F. on the 10th day. Examination of the lungs at that time revealed hyperresonance with absence of breath sounds over the entire right lung field, except for the base where the percussion note was dull, but the breath sounds absent. This suggested a hydro- or pyopneumothorax and the Roentgen ray film of the chest confirmed this suspicion. It showed a pneumothorax on the right with approximately 30% compression of the lung and a fluid level in the pleural cavity at the level of the seventh rib posteriorly; the left lung field was clear (Fig. 2). Thoracocentesis revealed the presence of a small amount of straw-colored fluid. The patient continued to run a septic course with rapidly progressing general failure. His temperature went up to 105° F. Thoracocentesis was repeated and again yielded clear fluid. No organisms were found in both specimens of pleural effusion on smear or culture and later the guinea-pig inoculation tests were reported as negative



Fig. 2.—Case 2. Right pneumothorax and fluid.

on the same specimen. No tumor cells were seen in the centrifuged sample. Sputum was repeatedly negative for acid-fast organisms and tuberculin injected intracutaneously did not give a positive reaction. Another blood culture taken on January 6 failed to reveal any growth. On the same day the total leukocyte count was found to have mounted to 17,200 (94% neutrophils) with marked "shift to the left."

The patient expired on Jan. 12, 1944, 22 days after admission.

*Autopsy.* The pleural cavities contained no excess of free fluid. The right lung was found to be partially collapsed and adherent along its posterior surface to the chest wall by moderately dense fibrous adhesions. The lung weighed 500 gm., with dull and granular surfaces covered with fibrin, and presented the usual appearance of bronchopneumonia. The bronchial mucosa was congested and the bronchi were partially filled with purulent exudate. The pulmonary vessels were patent. The heart weighed 300 gm., and on dissecting the organ a soft, friable, reddish-brown, smooth-surfaced vegetation, varying from 4 to 6 mm. across, could be seen in midportion of each cusp of the aortic valve along the line of closure; these were firmly attached to the valve. A

similar vegetation, measuring 6 mm. in its greatest diameter, was found along the line of closure of the aortic cusp of the mitral valve.

*Anatomic Diagnoses.* (1) Pneumonia, bronchial, unresolved; (2) pleuritis, acute; (3) pneumothorax; (4) endocarditis, acute, bacterial.

**Discussion.** In the 2 cases presently reported spontaneous pneumothorax occurred as a complication of pneumonia, in 1 instance being accompanied by sterile pleural effusion. In 1 of these cases the possibility of tuberculosis as an underlying process responsible for this occurrence was rather definitely ruled out by repeated studies of the sputum by smear, culture and guinea-pig inoculation, as well as the subsequent clinical course with serial Roentgen ray studies. In the other case the autopsy findings conclusively eliminated the presence of a Koch's infection.

From the review of the scant literature on the subject, along with the study of the cases here reported, it appears that spontaneous pneumothorax occurring in association with pneumonia may be classified into two varieties: (1) with or without serous effusion, presumably sterile; (2) associated with empyema. The first variety represents a comparatively innocuous complication, not in itself fraught with any disastrous consequences, and usually ending in recovery with uneventful absorption of the air from the pleural cavity. It apparently represents the closed type of pneumothorax; that is, the pulmonary fistula which creates it is probably of a small caliber and as a result it very often closes with the retraction of expiration and opens again in the succeeding inspiration, giving rise to the valvular effect. The etiology of this variety of pneumothorax is debatable. At least a partial clue may be found in the explanation Pierce and Dirkse<sup>15</sup> give for the formation of pulmonary pneumatocoele and pulmonary cysts. These authors believe that a certain sequence of events in the course of an antecedent pulmonary infection offers a more logical explanation for the origin of multiple cystic disease of the lungs than congenital abnormalities. They maintain that since necrosis of the bronchiolar walls associated with small abscesses arising in these structures is a relatively frequent occurrence in the course of a bronchopneumonia, the rupture of alveolar or bronchiolar walls with the production of an interstitial emphysema may occur. This would afford opportunity for air to dissect along the septa during cough, with the formation of subpleural blebs. "With the bronchial infection there is an interstitial inflammation, as contrasted with the intra-alveolar infection of the lobar type. Peribronchial alveoli become involved. The peripheral alveoli may be affected secondary to the changes in bronchi and bronchioles, or obstructed by the exudate in the latter. The tendency to confluence of involved lobular areas is common, often with acutely emphysematous intervening lobules due to partial obstruction of the proximal bronchus or bronchiole by exudate and inflammation. There is then, in association with bronchopneumonia, a ready opportunity, depending upon the dominant lesion, for the development of: (a) a sacular to cystic bronchiectasis by means of the damage to the bronchiole and bronchiolar walls; or (b) focal acute lobular vesicular emphysema

which may not be relieved because of incomplete resolution in or repair of the proximal airway; or (c) peripheral bullous (subpleural) emphysema by means of the rupture of the bronchial walls which permit an escape of air into the interstices . . . . The term pneumatocele properly denotes the tumorous nature of the air-filled dilated or ectatic alveoli or lobular spaces, corresponding to singular or multilocular character assumed respectively by the emphysematous air spaces. Our concept of the origin of the pneumatocele is the acute lobular emphysema associated with lobular pneumonia. A persistent check-valve obstruction of the bronchial lumen we believe to be due to either non-resolution of the initial inflammation of the bronchus or a subsequent distortion by the dilated air spaces." It is not difficult to conceive how a severe paroxysm of coughing may lead to the rupture of such a pneumatocele formed in the course of a bronchopneumonia, this leading to formation of spontaneous pneumothorax.

In the second variety of pneumothorax complicating pneumonia and associated with empyema, the simple pneumothorax may quickly evolve into pyopneumothorax. The pathogenesis of this variety is easily understandable as the situation resembles that of a pulmonary abscess or tuberculosis. It represents an open pneumothorax; the fistulous opening is larger, caused by the breaking down of an infected pulmonary focus, and does not close in expiration. Both varieties may be ushered in by a picture of an acute respiratory crisis, or, masked by the other grave symptoms of the underlying pneumonic process, may pass unnoticed.

**Summary.** 1. Spontaneous pneumothorax may occur as a complication of pneumonia in adults leading to the unwarranted suspicion of tuberculosis.

2. The literature on the subject is rather scant, containing 20 reported cases; 2 cases here presented bring the total of reported cases to 22.

3. This complication of pneumonia in adults is not commonly known and in spite of the scarcity of the reported cases probably occurs more frequently than is apparent from the review of literature. The fact that this occurrence, being masked by the other grave symptoms of the underlying pneumonic process, may not constitute a distinct or dramatic episode in the course of a pneumonia, accounts for the failure in more frequent recognition of this complication. With serial Roentgen ray studies it may be found to happen much oftener than noted heretofore.

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## THE HEPATOTOXIC ACTION OF DIETHYLSTILBESTROL WITH REPORT OF A CASE

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SINCE the original publications on synthetic estrogens by Dodds and his associates<sup>3,4</sup> in 1938, much experimental and clinical study has been devoted to these substances, and a "vast literature" has been built up.

The therapeutic effects of one of these synthetic substances, diethylstilbestrol (4,4'-dihydroxy-a:B-diethylstilbene), were found in general to be similar to those of natural estrogens; of great import was the observation that this new agent was strongly potent when administered orally. It was further noted that various extragenital effects were produced in animals, and particular attention was focused on the liver as being especially vulnerable to fatty degeneration and necrosis.<sup>1,8,13,14,15,18</sup> When diethylstilbestrol was tried in humans, the implication of hepatic impairment seemed strengthened by numerous reports of unfavorable symptoms, such as nausea, vomiting, dizziness, and malaise; the incidence of such side reactions varied from 5 to 80% in different series.<sup>5,16,19</sup> However, after many studies of hepatic function performed by various groups employing diethylstilbestrol clinically, the general conclusion was reached that the drug was not an hepatotoxic agent when used in therapeutic doses.<sup>6,7,9,17</sup>

Aside from the unpleasant systemic side effects just mentioned, several severe reactions to diethylstilbestrol have been reported, most of them apparently being on an allergic basis. These include a case of exfoliative dermatitis, described by Kasselberg and Memphis;<sup>12</sup> a case of severe angioneurotic edema, by Saphir and Weinglass;<sup>20</sup> and

1 case of angioneurotic edema, 1 of herpetic eruption and 4 of mild rash associated with faintness and dizziness, by Cohen and Cohen.<sup>2</sup>

We present herewith a case of hepatocellular jaundice occurring after diethylstilbestrol administration. A study of this and of other cases demonstrated an allergy to be the underlying factor. To our knowledge, no similar instance of definite hepatic impairment in the human has been reported.

**Case Report.** H. W., a 44 year old colored female, was admitted to the Medical Service of the Metropolitan Hospital on May 26, 1942, for jaundice, nausea and epigastric pain. Eight days previously the patient had begun to experience vague epigastric pain and nausea, and 4 days later jaundice was noted, with the urine becoming dark and the stools grayish. There had been frequent episodes of "indigestion" and marked constipation during that week.

The patient had presented herself several weeks earlier at the Gynecological Clinic for complaints associated with the menopause, namely nervousness, palpitation, insomnia, hot flushes, and transitory arthralgias, all present since the early part of 1940. Diethylstilbestrol was prescribed, 1 mg. every other day, but the patient did not adhere strictly to this régime, and by the time of admission she had taken 12 mg. over a 14-day period. The nausea and epigastric discomfort were first noted 8 days, and the jaundice 12 days, after medication had been begun. Pruritus was never present.

The patient's last menstrual period occurred in December 1941. She had a 16 year old son, alive and well, and 3 miscarriages subsequent to his birth. There was also a history suggestive of gonorrheal and possibly of luetic infection at the age of 17 or 18.

TABLE 1.—LABORATORY DATA—PATIENT H. W.

Date	Icterus index	Van den Bergh	Ceph. flocc.	Phosphatase	Total serum prot.	Serum alb.	Serum glob.	Total serum chol.	Chol. esters	Free chol.	Kahn test	Urine		W.B.C. (thous. per c.mm.)	Other data
1942												Bile	Urobilin		
5-27	65.0	Biph.	4+	4.0	7.32	3.46	3.86	100	36	64	4+	Pos.	Neg.		Wass. neg.
5-29	65.0	Biph.	4+									Pos.	Neg.	4.4	
6- 3	34.0	Del.	4+	3.0	6.40	3.12	3.28	140	70	70	3+	Neg.	Incr.		Wass. neg.
6- 5	12.8	Del.	3+	3.0	8.02	2.31	5.71	85	37	48		Neg.	Incr.		
6- 8	10.8	Del.	3+	3.1	8.00	4.30	3.70	158	83	75	Neg.	Neg.	Incr.	4.5	Wass. neg.
6-10	11.9	Del.	3+	3.3	7.80	5.02	2.78	150	75	75	Neg.	Neg.	Norm.		Wass. neg.
6-24	8.1	Del.	4+	5.0	6.09	4.91	1.18	148	80	68		Neg.	Norm.		
7- 6	16.0	Del.	4+	3.7	8.02	3.17	4.85	150	80	70		Neg.	Norm.		
7-17	8.0	Neg.	Neg.	3.1	8.02	5.07	2.95	100	72	28	Neg.	Neg.	Norm.		Wass. neg.
8- 5	6.0	Neg.	Neg.	4.5	7.60	5.20	2.40	130	94	36		Neg.	Norm.		
8-10	6.5	Neg.	Neg.	4.0	6.02	4.63	1.39	100	56	44		Neg.	Norm.		
1943															
3-17	5.0	Neg.	Neg.	4.5	8.19	5.67	2.52	165	116	49	Neg.	Neg.	Norm.		Wass. neg.
4-26	5.0	Neg.	Neg.	3.9	7.83	5.04	2.79	139	99	40		Neg.	Norm.		
4-29	5.5	Neg.	Neg.	3.3	8.05	5.03	3.02	170	114	56	Neg.	Neg.	Norm.	7.3	Wass. neg.

On admission to the hospital, physical examination revealed a moderately obese middle-aged colored female appearing subacutely ill. The temperature, pulse and respiration were normal. Icterus of the skin, sclerae, and mucous membranes was distinctly perceptible. The liver edge was palpated 2 finger-breadths below the costal margin, and was somewhat tender. The spleen could not be felt. The remainder of the physical findings were not remarkable.

**Course.** Laboratory data obtained after admission (Table 1) presented definite evidence of diffuse intrahepatic involvement: jaundice, markedly positive cephalin flocculation, low total serum cholesterol, low percentage of cholesterol esters, and inversion of the albumin:globulin ratio. None of the

figures was characteristic, or even suggestive, of extrinsic biliary obstruction.<sup>21</sup> Roentgenographic studies inadvertently performed on June 11, when gross jaundice was still present and function tests indicated persistent involvement of the liver, revealed the gall bladder to be normal in size, shape and position; the test dye was well concentrated, and emptying occurred promptly following a fatty meal. There was no evidence of calculi.

The patient was treated with a diet low in fat content and high in carbohydrate, protein and vitamins, especially B-complex. This was supplemented by daily intravenous injections of 50% glucose. Clinical improvement occurred gradually, and concomitantly the laboratory findings reverted to normal. The patient left the hospital on August 5, 1942, refusing to stay until investigation of the etiologic factors responsible for her illness had been completed. A follow-up study was attempted, but the patient had disappeared. It was not until April 24, 1943, that we located her and induced her to reënter the hospital for further study. At this time she complained severely of recurrent menopausal symptomatology. There had been no further jaundice or epigastric pain.

**Procedure and Discussion.** In the belief that diethylstilbestrol might have been the cause of jaundice in this case, we began a systematic study. In view of the relatively small amount of drug taken by the patient, it did not seem reasonable to assume a *toxic* effect, and we were inclined to consider an allergic etiology, in accordance with the reports of Finch<sup>5</sup> and of Saphir and Weinglass,<sup>20</sup> who found positive intradermal reactions with dilute solutions of diethylstilbestrol. We therefore undertook to test our patient for sensitivity to this substance. The series of skin tests performed on her, in both 1942 and 1943, are detailed in Table 2.

TABLE 2.—SKIN TESTS DONE ON PATIENT H. W. ALL TESTS INTRADERMAL USING 0.1 CC. MATERIAL

Date	Testing material	Results
6-30-42 } 4-26-43 }	Diethylstilbestrol in corn oil*—1 mg. in 5 cc.	Negative
4-26-43	Corn oil*	Negative
4-26-43	Diethylstilbestrol propionate in corn oil*—1 mg. in 5 cc.	Negative
8- 1-42 } 4-26-43 }	Patient's own serum (fresh)	Negative
8- 1-42 } 5- 3-43 }	Patient's own serum incubated 48 hours at room temperature	Negative
8- 1-42 } 5- 3-43 }	Patient's own serum incubated 48 hours at room temperature with corn oil—equal amounts	Negative
5- 3-43	Suspension of crystalline diethylstilbestrol† in patient's own serum (1 mg. in 5 cc.) incubated 48 hours at room temperature	5 cm. wheal—red, tender, indurated
5- 3-43	Diethylstilbestrol in corn oil (1 mg. in 5 cc.), incubated 48 hours at room temperature with patient's own serum	6 cm. wheal—red, tender, indurated, with central papule → pustule in 3 days → central necrosis (see Fig. 1)

\* Supplied through courtesy of Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.

† Supplied through courtesy of E. R. Squibb & Sons, New York, N. Y.

In contrast to the findings of Saphir and Weinglass, we obtained no intradermal reaction in this patient when employing diethylstilbestrol alone. However, we did encounter a very severe response after incubating the crystalline diethylstilbestrol or diethylstilbestrol in corn oil with the serum of the patient for 48 hours. Besides the local reaction described in Table 2, the patient also exhibited a systemic response characterized by malaise, fever, chilliness, and discomfort in the region of the liver. The painful wheal at the injection site (Fig. 1) attained its maximal development in 36 hours, then regressed gradually and disappeared in 6 days. All the controls—diethylstilbestrol in corn oil, corn oil alone, the patient's fresh serum alone, the patient's serum incubated alone and with corn oil—gave completely negative results.

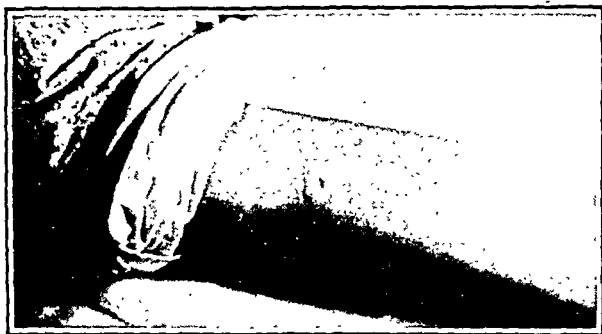


FIG. 1.—Skin reaction to diethylstilbestrol. Severity of reaction indicated by necrosis visible at center of wheal.

On the basis of these reactions, the conclusion is justified that diethylstilbestrol incubated with the patient's serum acted as an allergenic substance.

The question then arose as to whether diethylstilbestrol incubated with the sera of other patients exhibiting no clinical signs of allergy could cause similar effects in them, particularly if these patients had been treated beforehand with diethylstilbestrol. The tests undertaken to clarify this point are recorded in Table 3. It is notable that the results in all 9 patients were negative, regardless of whether they had previously taken diethylstilbestrol.

TABLE 3.—CONTROL PATIENTS—ALL TESTED WITH 0.2 CC. INTRADERMALLY OF DIETHYLSTILBESTROL IN CORN OIL INCUBATED 48 HOURS WITH PATIENT'S OWN SERUM (1 MG. IN 5 CC.)

Patient	Age	Menopausal symptoms	Oral stilbestrol taken	Result of skin test
F. M.	52	No	Never	No reaction
M. G.	45	Yes	Never	"
M. L.	40	Yes	Never	"
F. G.	52	Yes	1 mg. daily—5 mg. taken	"
G. H.	43	Yes	1 mg. daily—17 mg. taken	"
J. S.	75	No	1 mg. daily—2 mg. taken	"
M. R.	64	Yes	6 mg. (1 mg. daily) 7 days before testing	"
L. H.	58	Yes	8 mg. (1 mg. daily) 10 days before testing	"
M. M.	62	Yes	10 mg. (1 mg. daily) 4 days before testing	"

Experiments were not performed to determine whether the serum of the sensitive patient, when incubated with diethylstilbestrol, could cause a wheal in another patient, or, conversely, whether similarly prepared serum from another patient could produce a wheal in the sensitive one. Such tests might have shed light on the rôle of serum specificity as against patient susceptibility. Nevertheless, on the basis of those tests we were able to complete, it can be stated with certainty that our patient's serum, when incubated with diethylstilbestrol, had the capacity to produce an unknown substance which caused a severe local reaction as well as systemic signs similar to those occurring with the original illness.

A thorough elucidation of the findings in this case is as yet impossible, but several theoretical considerations deserve mention. Finch<sup>5</sup> has offered an interesting explanation for the nausea and vomiting of pregnancy; he postulated an allergic reaction of the patient to the secretion of her own gravid corpus luteum. Using this unidentified luteal hormone in cases of hyperemesis gravidarum, he obtained intradermal reactions such as we found on incubating diethylstilbestrol with serum. It is interesting that patients with nausea and vomiting due to diethylstilbestrol responded to his luteal hormone exactly as did hyperemetic pregnant women. If, however, diethylstilbestrol administration had occasioned no untoward effects, the patients exhibited *no* intradermal reaction to the luteal hormone. Conversely, Finch found that diethylstilbestrol in oil alone produced no skin reaction, just as in our case, although he could desensitize positive reactors against the luteal hormone and against diethylstilbestrol as well. He explained the tolerance of males and of young girls to diethylstilbestrol on the basis of their never having been sensitized to the luteal hormone; the tolerance of normal pregnant women he attributed to an antihormone effect of progesterin.

Finch regarded diethylstilbestrol not as a toxic substance *per se*, but rather as an allergen. Although such a concept is probably correct, it might be more correct to say that only the "sensitive" patient can form the final allergenic substance in sufficient quantity to produce clinical effects. It has been proposed that the untoward reactions to diethylstilbestrol may be due to abnormal breakdown within the body. Zondek and his co-workers,<sup>22</sup> however, feel that normally the liver inactivates diethylstilbestrol more slowly than it does estrone, thus accounting for both the greater oral efficacy and the frequency of untoward reactions. Accordingly, they advise caution in the use of diethylstilbestrol when hepatic reserve is diminished.

The serologic findings in our case (Table 1) demonstrate that at least part of the hepatic dysfunction is manifested in disturbance of the protein fractions. This is indicated first by the positive cephalin flocculation, originally postulated by Hanger<sup>10</sup> as being due to abnormal globulins, but more recently<sup>11</sup> attributed to albumin alterations. Furthermore, although the Wassermann reaction was consistently negative, the Kahn test was strongly positive during the acute phase

of illness. Since the serum globulin fraction was at no time excessively elevated, and the albumin only moderately decreased, a *qualitative* alteration of these fractions may be the basis not only for the positive Hanger and Kahn reactions, but also for the antigen-antibody mechanism in the patient's allergic response to diethylstilbestrol.

In reporting this case of hepatocellular jaundice, we certainly have no desire to malign so valuable a substance as diethylstilbestrol. However, now that this synthetic agent is being so extensively employed for a wide variety of conditions, it seems wise to sound a warning that diethylstilbestrol in moderate dosage *can* cause severe hepatic damage in the human.

**Conclusions and Summary.** 1. A woman with severe hepatic damage occurring after administration of diethylstilbestrol in moderate dosage was demonstrated to be allergic to a substance formed by incubation of diethylstilbestrol with the serum of the patient.

2. All possible controls were negative. Furthermore, similarly incubated sera of other patients produced no reaction when injected intradermally in the same subjects from whom they were taken.

3. The mechanism of untoward reactions associated with diethylstilbestrol medication is discussed, and reference is made to its relationship to the toxic complications of pregnancy.

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THE ENHANCEMENT OF THE PLASMA CONCENTRATION OF  
PENICILLIN IN DOGS BY THE SIMULTANEOUS ADMINIS-  
TRATION OF PARA-AMINOHIPPURIC ACID, III

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THIS is the third of a series of papers concerning the effect of the simultaneous administration of the sodium salt of p-aminohippuric acid (PAH) and penicillin upon the plasma concentration and renal elimination of penicillin. Following the first brief announcement,<sup>4</sup> the second article<sup>3</sup> presented evidence indicating that when PAH was infused continuously by venoclysis the intravenous injection of single doses of penicillin resulted in: (1) a prolonged maintenance of a determinable plasma concentration of penicillin, and (2) a marked extension of the period during which penicillin was excreted in the urine, as well as a definite decrease in the rate of excretion and the total amount of penicillin recovered thereby per unit time.

The evidence supported the conclusion that this effect was brought about by a competition between PAH and penicillin for the same excretory mechanism of the renal tubular epithelium, since the clearance of penicillin (which normally approximates the renal plasma flow of dogs) could be depressed to or below values for the glomerular filtration rate by the simultaneous intravenous administration of PAH. The plasma concentrations of the latter compound which were found to produce this effect were above those resulting in maximal clearance values for PAH.

Toxicologic studies have indicated that this drug has an extremely low toxicity for animals. Pharmacologic investigations have shown venoclysis to be the most satisfactory mode of administration of PAH, although adequate, sustained plasma concentrations of the drug can be maintained by repeated subcutaneous or intramuscular administration, but not per os.<sup>6a,b</sup>

Although the earlier experiments wherein single intravenous doses of penicillin were administered showed quite adequately the inhibition of penicillin excretion by the administration of PAH, it remained for us to demonstrate the operation of this mechanism in experiments in which both penicillin and PAH were continuously infused over an extended period of time. It was thought that the continuous intravenous infusion of penicillin alone and penicillin with PAH might

yield data permitting a more accurate appraisal of the competitive affinities of these two substances for the same renal intracellular transport system and its practical importance, under laboratory conditions more closely paralleling the clinical application of the combined use of penicillin and PAH. Such experiments also would permit a histopathologic evaluation of cellular damage resulting from the use of these substances over a prolonged period of time. To this end, experiments were designed wherein penicillin alone or penicillin and PAH were infused continuously over periods of 36 to 54 hours.

**Procedure.** The methods for the assay of penicillin and the determination of p-aminohippuric acid, the apparatus used in the aseptic collection of urine and the general procedure in these experiments have been described in detail.<sup>3</sup> Very briefly, strict adherence to standard bacteriologic and surgical procedures were necessary for the collection of urine and blood samples. The modified Rammelkamp assay for penicillin<sup>7</sup> used in these experiments dictated these precautions.

Blood samples also were taken periodically for the determination of hemoglobin, hematocrit, plasma protein and albumin, total erythrocyte and leukocyte counts, and differential white cell counts. In the case of the earlier experiments described herein control animals, treated exactly as the test animals, except for the absence of PAH and penicillin in the infusion solutions, were maintained for the duration of the 48 hours to determine the effect of the barbiturate used to sedate the animals, water balance, the frequent bleedings, and so forth on the overall welfare of the animals. Hematologic studies, creatinine clearances, gross and microscopic tissue examinations, records of rectal temperature, heart rate, and so forth, were carried out as carefully on the control as the test animals. We found it advantageous to keep the dogs sedated by the injection of a barbiturate as frequently as indicated by the reactions of the animals to venipuncture and urine collections. Since the barbiturate caused a relaxation of the urethra, it was necessary to do a suprapubic exposure and ligation of the urethra just inferior to the neck of the bladder when the catheter was in place. This was done to avoid the extravasation of urine around the catheter.

**Experimental.** *Experiments Wherein Both Penicillin and PAH were infused for 48 hours.* In the first 2 experiments penicillin and PAH contained in the same infusion fluid were administered continuously by venoclysis over a period of 48 hours. The concentrations were calculated so that 15 Oxford units of penicillin and sufficient PAH to maintain the plasma concentration at about 30 mg./100 cc. were administered when the rate of infusion was 3 cc./min. This infusion fluid consisted of 1.5% sodium p-aminohippurate, 0.45% sodium chloride and 5 units/cc. of penicillin in distilled water, buffered at pH 7.4.

In both experiments, a priming dose of 120 mg./kg. of 20% sodium p-aminohippurate solution was injected intravenously. This was followed immediately by an infusion of the composition described above but containing no penicillin. After a 15-minute period for equilibration of PAH plasma concentration, a priming dose of penicillin was injected intravenously and the infusion of the solution containing both PAH and penicillin was begun. Dog 113 received 5300 units and Dog 39 received 2600 units of penicillin in the initial intravenous injections of this material. The average rate of penicillin infusion



was determined to be 14.4 units/min. for Dog 113 and 12 units/min. for Dog 39. These rates of infusion were of a magnitude which was calculated from previous data to give plasma concentrations of pen-

TABLE 1.—RESULTS AFTER PENICILLIN AND PAH, CONTAINED IN THE SAME INFUSION FLUID, WERE ADMINISTERED CONTINUOUSLY BY VENOCLYSIS FOR THE DURATION OF THE TESTS

Hours	Penicillin plasma conc. (units/cc.)	PAH plasma conc. (mg./100 cc.)	Penicillin clearance (cc./min.)	PAH clearance (cc./min.)	Urine (vol./min.)	Penicillin progressive percentage recovery
Dog 113, 14 kg.						
2*	.22	40.8	25.2	64.9	0.2	28.4
4*	.11	38.7	44.5	40.7	0.4	31.5
6	.09	23.1	69.4	97.3	2.3	30.3
8	.09	28.7	52.4	70.2	0.5	30.4
10	.09	26.9	175.0	152.8	3.6	32.0
12	.09	24.2	69.1	129.5	2.5	32.7
14	.09	25.1	119.9	133.5	2.9	34.2
16	.055	26.4	137.7	94.8	2.4	38.2
18	.056	23.1	84.5	69.3	1.4	42.1
20	.09	26.6	148.5	117.4	2.6	45.3
22	.09	26.0	173.8	133.4	3.3	47.9
25	.00	24.0	..	94.5	1.3	50.7
27	.055	16.7	284.9	113.6	1.7	51.8
29	.055	26.0	222.7	111.1	1.0	52.7
31	.11	27.3	169.3	90.3	2.3	58.7
33	.09	56.8	131.3	66.3	3.6	61.9
35	.09	36.5	127.3	126.0	3.4	65.0
37	.055	33.3	142.2	101.6	0.9	64.5
39	.055	29.3	189.8	63.0	1.7	64.8
41	.17	33.7	103.8	86.5	2.1	64.9
43	.17	33.4	99.7	107.1	3.7	65.7
45	.17	40.4	67.2	99.0	2.0	66.2
47	.055	38.5	103.6	93.1	2.0	65.3
48	.09	35.2	81.1	87.5	3.0	65.1
Av.	.093	30.9	122.7	97.6	2.1	65.1
Dog 39, 14.2 kg.						
2*	.17	40.0	79.3	83.1	1.3	48.1
4	.11	35.1	108.1	105.0	2.2	59.8
6	.11	31.5	105.3	104.4	2.1	64.5
8	.088	22.1	147.5	148.4	1.2	63.6
10	.089	24.8	80.5	109.9	0.7	63.7
12	.00	28.2	..	82.3	0.6	61.9
14	.088	26.5	63.0	68.6	0.2	59.6
16	.055	30.1	187.1	87.6	0.6	59.7
18	.055	29.2	227.2	141.9	1.1	61.5
20	.055	33.5	245.0	116.9	1.3	61.4
22	.055	31.5	338.5	161.3	1.4	61.3
24	.055	27.5	160.1	123.3	1.1	60.8
26	.089	24.4	185.1	189.1	1.8	62.4
28	.088	22.4	163.1	118.1	1.0	65.1
30	.089	23.5	179.4	132.8	1.7	67.3
32	.088	25.6	135.0	118.2	4.9	68.6
34	.13	34.6	105.6	95.4	1.3	70.9
36	.089	29.2	90.0	89.3	1.7	73.0
38	.088	26.1	96.7	115.6	3.1	72.5
40	.088	30.4	116.9	78.9	1.3	72.5
42	.087	29.1	152.0	113.0	1.2	73.1
44	.088	30.0	156.0	127.6	1.3	73.7
46	.13	31.5	84.4	82.1	0.7	74.6
48	.088	28.2	54.0	62.5	0.4	74.4
Av.	.086	29.0	141.7	110.2	1.4	74.4

\* Omitted from average.

icillin of about 0.025 units/cc. when no PAH was administered and about 0.1 units per cc. when sufficient PAH was infused to maintain a plasma concentration of approximately 30 mg./100 cc. A condensation of the data obtained in these 2 experiments is given in Table 1.

Before discussing the results of these experiments in any detail certain general considerations of the work should be presented. In these experiments control of the rate of infusion was obtained by regulating the number of drops of fluid which passed through the filter per minute. It is not surprising therefore that the plasma concentrations of both substances should have varied. An uncontrollable feature of the set-up was that as the rate of infusion decreased the plasma penicillin level dropped, both because of the decreased rate of infusion of the antibiotic substance and because of its increased tubular excretion, due to the fall in plasma PAH concentration. Conversely, as the rate of infusion was increased to raise the lowered PAH concentration the plasma penicillin level was increased incommensurately. This point is illustrated in the data presented in Table 1.

Considering the data on both dogs together, several points appear to have been established satisfactorily. As long as the rate of infusion was kept constant, judging by the PAH plasma concentration, the penicillin plasma concentration remained at about 0.09 units/cc. (Dog 113) or slightly below that in Dog 39 where the rate of infusion was correspondingly less (12 units/cc.). The plasma concentration varied somewhat as might be expected considering the method of rate control, the type of assay, and the effect of PAH on penicillin clearance.

The penicillin clearance was usually greater than the glomerular filtration rates for the animals (81.1 cc./min. for Dog 113 and 78.2 cc./min. for Dog 39), but approximated the minimal renal plasma flow of such animals only in a few instances at which time the plasma concentration of penicillin was also decreased. Thus the tubular excretion of penicillin was diminished but not abolished by PAH, except possibly at the beginning of the experiments.

At very low plasma concentration the renal clearance of PAH approximates the minimal renal plasma flow of man<sup>9</sup> and dogs,<sup>5</sup> which in the latter instance exceeds 200 cc./min. for animals of this weight. However, as the load on the tubules is increased by raising the plasma concentration of PAH its renal clearance is suppressed as is the case in these data.

It may be noted that the urine flow did not equal consistently the rate of infusion. This was due in part to the amount of sodium chloride that was added to the fluid in addition to the sodium p-aminohippurate and penicillin-sodium. It follows that the obvious, and actually the most important, finding before and after autopsy was tissue edema.

In these 2 dogs, 65.1 and 74.4% of the penicillin injected appeared in the urine during the course of the experiment. Of this amount, 28.4 and 48.1% was excreted in the first 2 hours following the priming doses in the course of the progressive recoveries. More important,

than the actual figures is the fact that not all of that which was injected was ultimately recovered, which probably means that a certain amount of the material was inactivated or eliminated by another route. This observation is in confirmation of the earlier reports of Abraham, Florey and associates,<sup>1</sup> Rammelkamp and Keefer<sup>2</sup> and ourselves.<sup>3</sup>

The hematologic and toxicologic findings in all the experiments will be considered together, later in this report.

*The effect of increasing the rate of infusion of penicillin on plasma concentration and clearance of the antibiotic substance, 36-hour experiments.* The purposes of these tests were to determine the effect of increasing the rate of infusion of penicillin on its plasma concentration and also the actual plasma values obtained when penicillin was infused at different rates, in addition to serving as toxicologic controls on the 48-hour PAH experiments.

The experiments were designed so that an initial intravenous injection of 1000 Oxford units of penicillin was immediately followed by the intravenous infusion at 15 units/min. of penicillin in a solution containing 0.22% NaCl and 3.75% glucose. This was injected at a rate of 1 cc. per minute with the aid of an electrically driven mechanical injection apparatus. The same solution containing no penicillin was infused at a different site by "drip" at a rate of 2 cc./min. Thus the same vol./min. was injected in all the experiments. Duplicate creatinine clearances were performed every 12 hours during the experiments. The initial (15 units/min.) rate of infusion was maintained for 16 hours to permit more than adequate time for equilibration of the plasma concentration. Immediately after the 16-hour clearance, the concentration of penicillin in the infusion was doubled to permit the infusion of 30 units/cc./min. Ten hours later the concentration of penicillin in the infusion solutions was doubled again so that for the last 10 hours of the experiment the rate of infusion was 60 units/cc./min.

Unfortunately, the conditions under which this set of experiments were performed were sufficiently different from those obtained during the other types of experiments as to make these useless as quantitative controls on the previous ones in which penicillin and PAH were infused together. Because of the uniformity of the electrically driven infusion of penicillin, these dogs received a greater average amount of penicillin at a more regular rate than in the previous experiments. Moreover, there is reason to believe that a faulty standard penicillin solution was employed to set the values in the penicillin assays. These facts, though minimizing the comparative usefulness of the first 16 hours of these experiments, do not invalidate the differences resulting from increasing the dosage of penicillin within these experiments.

A condensation of the data is presented in Table 2. Increasing the rate of infusion of penicillin from 15 to 30 units per minute increased the plasma concentration of the antibiotic agent in all 3 experiments. Considering average values alone, there was a twofold or greater increase in the plasma penicillin concentration when the rate of infusion was increased from 15 to 30 units per minute. A second increase in

TABLE 2.—RESULTS AFTER A SUMMARY OF DATA ON EXPERIMENTS WHEREIN PENICILLIN, ADMINISTERED CONTINUOUSLY BY VENOCLYSIS, WAS INCREASED PERIODICALLY BY DOUBLING ITS CONCENTRATION IN THE INFUSION FLUID

Hours	Dog 86, 13.6 kg.				Dog 117, 20.5 kg.				Dog 102, 18.6 kg.			
	Penicillin plasma concentration (units/cc.)	Penicillin renal clearance (cc./min.)	Urine volume (cc./min.)	Rate of Continuous Intravenous Infusion = 1000 Units of Penicillin.	Penicillin plasma concentration (units/cc.)	Penicillin renal clearance (cc./min.)	Urine volume (cc./min.)	Rate of Continuous Intravenous Infusion = 15 Units/Min.	Penicillin plasma concentration (units/cc.)	Penicillin renal clearance (cc./min.)	Urine volume (cc./min.)	Rate of Continuous Intravenous Infusion = 30 Units/Min.
	Initial Intravenous Injection											
1*	.130	126.7	0.2	.074	.074	97.0	0.8	.090	.090	321.1	0.4	.146
2	.089	121.5	4.5	.038	.038	87.9	0.7	.041	.041	334.1	0.3	.047*
4	.045	452.9	3.9	.037	.037	270.0	0.9	.210*	.210*	35.3*	3.3	.146
6	.090	108.2	2.4	.037	.037			.093	.093	193.5	0.9	.137
8	.045	194.0	1.8	.036	.036	260.0	1.5	.093	.093	224.7	1.3	.125
10	.094	128.7	1.4	.037	.037	464.1	3.6	.093	.093	136.6	1.9	.139
12	.092	98.8	2.4	.037	.037	255.0	1.0	.093	.093	481.7	3.0	
14	.043	206.5	0.9	.035	.035	330.8	0.8	.042	.042	91.4	0.2	
16	.044	284.9	1.8	.037	.037	348.6	1.6	.094	.094	112.8	2.8	
Av.	.068	199.4	2.4	.037	.037	288.1	1.4	.078	.078	225.0	1.7	
Rate of Continuous Intravenous Infusion Increased to 30 Units/Min.												
18	.130	161.2	2.7	.160	.160	161.2	4.7	.146	.146	171.9	5.2	
20	.190	130.2	1.8	.110	.110	231.1	1.6	.047*	.047*	223.2	0.4	
22	.140	281.6	2.4	.150	.150	151.7	1.2	.146	.146	243.7	0.9	
24	.160	439.8	5.5	.160	.160	183.4	3.2	.137	.137	148.1	1.6	
26	.086	339.5	2.4	.140	.140	126.0	0.5	.125	.125	205.1	3.7	
Av.	.141	270.5	3.0	.140	.140	170.7	2.2	.139	.139	198.4	2.4	
Rate of Continuous Intravenous Infusion Increased to 60 Units/Min.												
28	.190	438.0	2.3	.190*	.190*	227.7	1.1	.185	.185	256.2	3.5	
30	.180	487.7	3.1	.190*	.190*	177.4	1.2	.143	.143	259.3	2.8	
32	.180	591.7	1.0	.300	.300	151.1	2.3	.190	.190	262.1	0.9	
34	.190	559.5	2.1	.300	.300	262.2	1.0	.281	.281	195.3	1.3	
36	.210	328.0	0.8	.310	.310	252.3	0.9	.210	.210	204.4	0.6	
Av.	.190	481.0	1.9	.300	.300	214.1	1.3	.202	.202	233.5	1.8	

\* Omitted from averages.

the rate of infusion from 30 to 60 units per minute likewise increased the plasma concentration of penicillin in all the experiments, but doubled the value in a single experiment. The clearance data indicated that the capacity of the renal tubular epithelium to remove completely penicillin from the plasma supplied to them was not exceeded in any of these experiments, for there was no depression in the clearance of penicillin as the plasma concentration was raised or the amount infused per minute was quadrupled.

Sufficient data are presented that one may calculate the amount of penicillin excreted per unit time. By doing so it can be shown that except for Dog 117, as the rate of infusion was doubled, the amount of penicillin excreted per minute was approximately doubled. The glomerular filtration rates (creatinine clearance) of the dogs did not vary significantly during the experiments.

*The effect of increasing the plasma concentration of PAH on the plasma concentration of penicillin when the rate of infusion of penicillin remained constant.* Since these were probably the most critical of our animal experiments, from the standpoint of clinical significance, it is proper that they should be presented last in the overall program of the penicillin-PAH research on dogs. A study of the accompanying figures, 1 through 4, will reveal the nature of the experiments. In concept they consisted of a control equilibrium phase wherein penicillin but no PAH was infused, followed by steplike periods of increasing PAH plasma concentration. Finally, the PAH plasma concentration was allowed to fall by discontinuing its injection. During the whole of the experiments the rate and unitage of penicillin injected remained constant.

In more detail, the infusion fluid contained in addition to penicillin or sodium p-aminohippurate 0.22% sodium chloride and 3.75% glucose. Penicillin was added to a portion of the infusion fluid and was injected by an electrically driven instrument delivering 1 cc./min. which contained 15 units of penicillin. The solution containing no PAH was infused by "drip" at a rate of 2 cc./min. during the control portion of the experiments. To this the amount of sodium p-aminohippurate necessary to produce the desired plasma concentration was added. The control period was 18 hours in one experiment and 20 hours in the other. The duration of injection of PAH to produce a given plasma level varied from 8 to 12 hours. To establish the various plasma levels of PAH single priming doses of 20% concentration were injected immediately after the last clearance at the preceding level. Thus the plasma levels were quickly increased, the concentrations of PAH in the infusion fluid being just the amount necessary to maintain the level at the desired plane. The data on the first of these experiments are presented in Figures 1 and 2. The data on the second experiment are presented in Figures 3 and 4.

The priming dose of penicillin in the first test (Dog 63) was 5000 units and the actual rate of infusion was 13.3 units/min. instead of the calculated 15 units/min. Probably because of the high priming dose a period of 12 hours was necessary in the case of Dog 63 (Fig. 1) before

the basal plasma concentration of about 0.025 units of penicillin/cc. was attained. Once attained it remained constant for at least 6 hours. During the first 2 hours after the infusion of PAH was begun the plasma concentration increased to 0.062 units/cc. where it remained constant as the plasma concentration of PAH was maintained at about 30 mg./100 cc. In the next period lasting from the 26th to the 36th hour of the experiment the PAH plasma concentration was increased to  $80 \pm 10$  mg./100 cc. There was a concomitant increase in the penicillin plasma concentration to 0.089 units/cc. In the final period the concentration of PAH was increased to  $110 \pm 5$  mg./100 cc. There was a lag of 4 hours before the penicillin plasma concentration began to rise again but it had attained a concentration of 0.17 units/cc. at the time the infusion of PAH was discontinued. As soon as the PAH was stopped the plasma concentration of both compounds began

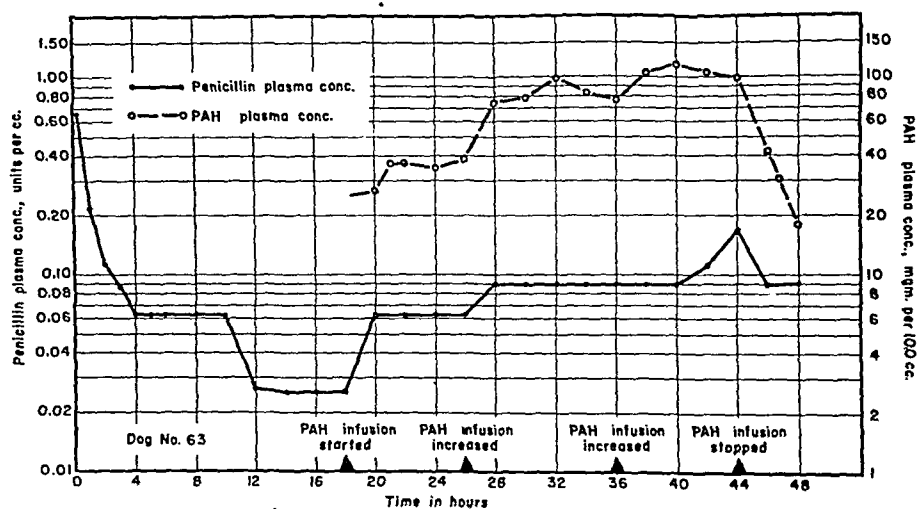


FIG. 1.—The effect of a stepwise increase in the p-aminohippuric acid plasma concentration on the level of penicillin in the plasma when it was administered continuously by venoclysis at a constant rate of 13.3 units/minute. The initial intravenous priming dose of penicillin-sodium was 5000 Oxford units. Dog 63.

to fall. The maximal penicillin plasma concentration attained was about 7 times the basal value when penicillin was infused alone.

Figure 2 shows the renal clearances of both PAH and penicillin during the course of the 48-hour experiments on Dog 63. We have frequently noted more or less cyclic fluctuations in the clearance of penicillin during these long-term experiments. These fluctuations were not necessarily associated with similar changes in urine flow. They were most exaggerated in the control phase of these experiments yet were perceptible even when PAH suppressed the overall clearance of penicillin. These changes were not associated with the administration of barbiturate and cannot be accounted for by errors in technique.

The administration of PAH depressed very strikingly the clearance of penicillin and tended to minimize its fluctuations. In general, as

the plasma concentration of PAH was increased the fluctuations in penicillin clearance decreased as did its maximal clearance within a given period. Also, as the PAH plasma concentration was raised its clearance decreased gradually. Again, it may be noted that on the whole these changes were independent of urine flow.

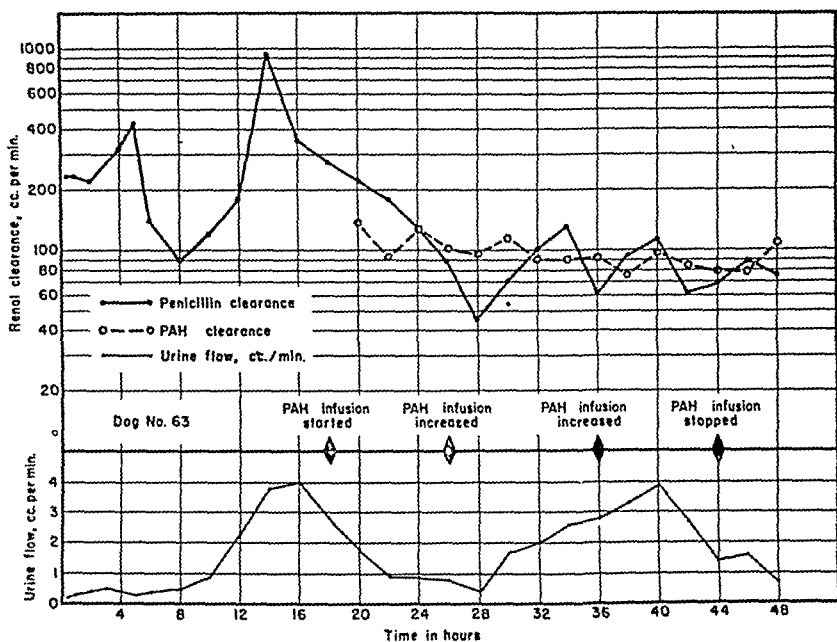


FIG. 2.—Renal clearance and urine flow data corresponding to the plasma level data presented in Figure 1, showing that as the plasma concentration of p-aminohippuric acid was elevated, stepwise the clearance of penicillin was markedly depressed and remained at a low level for the remainder of the experiment. Dog 63.

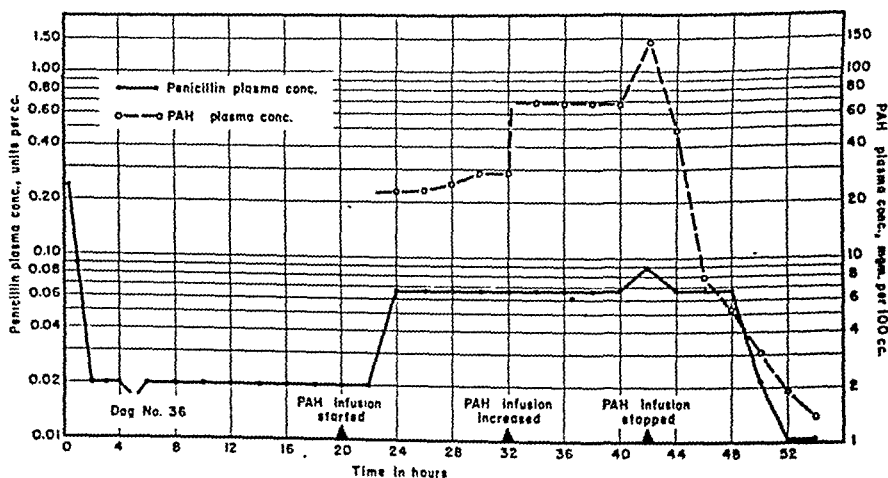


FIG. 3.—The effect of a stepwise increase in the p-aminohippuric acid plasma concentration on the level of penicillin in the plasma when it was administered continuously at a rate of 14.79 units/minute. The initial intravenous priming dose of penicillin sodium was 2500 Oxford units. Note that at the end of the experiment the plasma concentration of penicillin remained elevated until the plasma PAH concentration fell below 8 mg./100 cc., after which time it fell precipitously. Dog 36.

In the experiment on Dog 36 (Figs. 3 and 4) the priming dose of penicillin was decreased to 2500 units and the rate of infusion was 14.79 units per minute. It may be seen in Figure 3 that the period for the attainment of equilibrium in the control phase of the experiment was much shorter. For 20 hours, except for a technical error at the 5-hour period the plasma concentration was maintained at 0.02 unit/cc. when the rate of infusion was 14.79 units per minute. As soon as a plasma PAH concentration of  $25 \pm 3$  mg./100 cc. was attained the penicillin level in the plasma rose from 0.02 to 0.66 units/cc., more than a threefold increase. This was maintained for a period

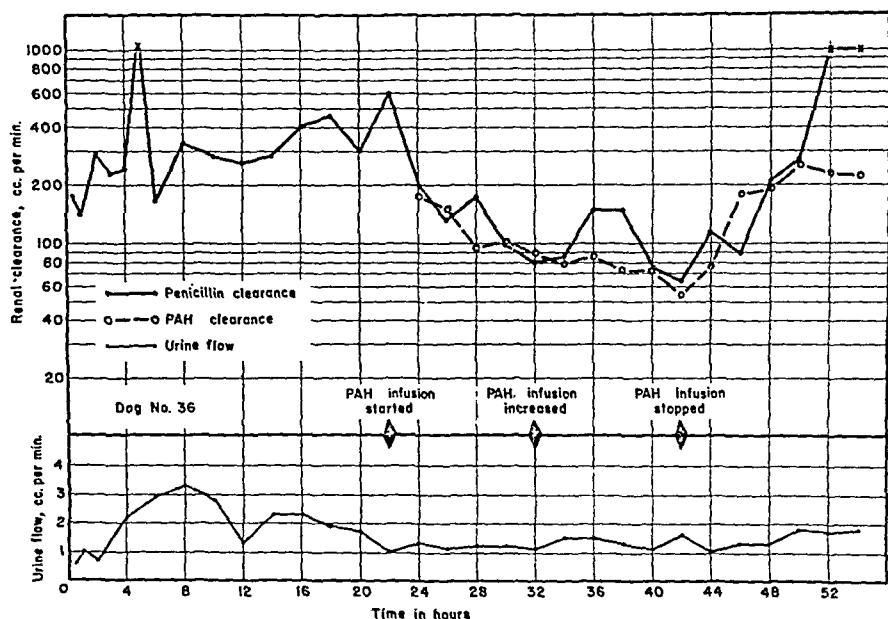


FIG. 4.—Renal clearance and urine flow data corresponding to the plasma level data presented in Figure 3, showing that as the p-aminohippuric acid plasma concentration was elevated stepwise the clearance of penicillin was markedly depressed and remained low until after the infusion of PAH was stopped. As the plasma concentration of PAH fell the clearance of both PAH and penicillin rose rapidly until they approximated renal plasma flow. The last two values for penicillin clearance could not be calculated since its plasma concentration was below the limits of the assay. Dog 36.

of 12 hours. A further increase in PAH plasma level to  $68 \pm 1$  mg./100 cc. did not increase the penicillin content in the plasma. Inadvertently, the plasma PAH concentration was markedly increased to about 145 mg./100 cc. at the end of the last 2-hour period of the PAH infusion. At that time the penicillin plasma level promptly increased to 0.089 units/cc.

This experiment was extended and penicillin administration was continued beyond the termination of the PAH infusion to follow the fall of the PAH plasma concentration and to determine the effect of that fall on the level of penicillin in the plasma. It may be seen that except for a prompt initial drop there was a lag period before the penicillin plasma concentration fell. However, 10 hours after the PAH was stopped (the 52-hour period) no penicillin was detectable



in the plasma and this was confirmed in the last 2 bleedings of the experiment. Thus the experiment demonstrated that we could both raise and lower the penicillin concentration of the plasma by raising and lowering the PAH plasma level, even when the rate of infusion of penicillin was maintained at such a low point as to produce only a barely determinable plasma concentration of the agent when no PAH was administered.

The curves presented in Figure 4 concerning the penicillin and PAH renal clearances are entirely consistent with the plasma findings shown in Table 3. During the control phase the clearance of penicillin fluctuated but was almost uniformly about 225 cc./min. As soon as the infusion of PAH was begun there was a precipitous fall in the renal clearance of penicillin. The trend of the penicillin clearance as well as PAH clearance continued downward as the plasma concentration of the latter compound was increased, reaching a low point of 54 cc./min. at the termination of the PAH infusion.

TABLE 3.—HEMATOLOGIC DATA

Some dogs received both penicillin and sodium p-aminohippurate continuously by venoclysis for a period of 48 hours; others received an infusion of penicillin for 36 hours; their corresponding controls received the infusion fluid without either penicillin or sodium p-aminohippurate acid for a similar period of time.

Dog No.	Hours*	Hemoglobin (gm./100 cc.)	Erythrocytes (millions)	Leukocytes (thousands)	Hematocrit (%)	Plasma protein (gm./100 cc.)	Plasma albumin (gm./100 cc.)	Remarks
81	0	15.0	6.9	19.0	51	6.6	..	Control dog with Dog 113
	24	11.4	5.4	22.4	39	5.5	2.5	
	48	10.2	4.4	16.4	33	4.9	2.3	
113	0	14.2	5.9	9.0	42	8.0	..	Received continuous intra-venous injection of PAH and penicillin
	24	14.1	6.0	13.2	50	4.4	2.6	
	48	12.6	5.5	15.7	40	3.7	2.0	
114	0	10.2	4.8	10.6	38	7.0	2.5	Control dog with Dog 39
	24	8.0	3.8	36.8	29	5.6	1.7	
	48	9.8	3.8	24.0	30	5.2	1.5	
39	0	15.7	7.5	5.8	53	5.8	4.0	Received continuous intra-venous injection of PAH and penicillin
	24	12.6	6.1	16.9	40	4.6	2.9	
	48	12.7	5.2	10.7	39	3.9	2.2	
86	0	14.8	7.5	20.0	48	5.9	3.7	Control dog with Dog 102
	24	15.1	7.3	20.2	51	5.8	3.8	
	36	14.4	6.2	14.0	46	5.7	3.1	
102	0	16.3	7.1	9.4	51	5.6	3.8	Received continuous intra-venous injection of penicillin for 36 hours
	24	12.4	5.8	17.9	44	4.9	3.0	
	36	13.7	6.5	17.5	47	3.8	2.1	

\* Hours after the experiment was begun at which the heparinized sample of blood was removed by venipuncture.

The clearances during the last 12 hours were proof, in our opinion, that there was no impairment of renal function by the materials administered during the experiment. It should be noted that as the plasma PAH level fell the clearance of both penicillin and PAH rose. The last determinable clearance of penicillin was 270 cc./min. at which time the clearance of PAH was 225 cc./min. The clearances of PAH during the last 2 periods of the experiment were 230 and 225 cc./min.

We believe that these values, together with the unaltered glomerular filtration rate, are the best possible evidence that can be offered for the absence of functional renal damage in these experiments, since they indicate that the ability of the tubules to clear completely the plasma of penicillin and PAH at low concentrations has not been impaired and that there was also no impairment of glomerular filtration, as evidenced by creatinine clearances.

*Toxicity.* The gross and microscopic findings in these and the corresponding control animals have been considered in some detail in another communication in this series.<sup>6b</sup> However, certain of the data can be presented more properly at this time. Table 3 presents condensations of hematologic studies on some of these dogs during the course of the experiments. When one considers the nature of the experiments, the greater input than output of fluids, the removal of up to 185 cc. of blood during the 48 hours, the numerous operative procedures that were carried out, and so forth, it is remarkable that the changes were no greater than observed. Hemoglobin values dropped in some cases and increased in other experiments. The greatest fall occurred in a control dog which received neither penicillin nor PAH. Also, the hematocrit decreased more in a control dog than in those which received penicillin and PAH. Total plasma proteins and albumin decreased in all the experiments which was not surprising considering the dilution effect and their removal by bleeding. A leukocytosis occurred in all the animals which was actually an increase in neutrophilic cells, resulting in a relative lymphocytopenia. This effect may be due partially to the wounds produced by surgery and possibly also by pyrogenic influences, such as the localized application of heat by means of an electric hot pad used to maintain proper body temperature.

As has been stated before, the most outstanding and only significant finding resulting from the experimentation was definite tissue edema. This was decreased somewhat by attention to the electrolyte content and the tonicity of the infusion fluids. The infusion rate of 3 cc./min. was in excess of the urine flow the dogs could maintain over a period of time but was deliberately used to minimize fluctuations in the PAH plasma concentration since we were forced to use a "drip" infusion method for the administration of that compound and also to avoid the use of unnecessarily hypertonic solutions when the plasma level of PAH was maintained at very high levels. Definite pathologic findings in the unselected dogs such as focal subcapsular renal abscesses and infectious granulomatous lesions were as frequent in the control as in the test animals and were not considered as being due to or influencing the experiments. A detailed description of the histopathologic findings will be described in the fourth report of this series.<sup>6b</sup>

Microscopic examination of the urine present in the bladder, ureters and renal pelvis, and in the urine that had been allowed to stand in the refrigerator overnight, did not reveal the presence of crystals of p-aminohippuric acid or its sodium salt. The histologic sections of the kidneys gave no evidence of the blocking of tubules by crystals,

**Comment.** In these experiments we have attempted to simulate as closely as practicable in the laboratory the initial clinical evaluation of the combined use of penicillin and sodium p-aminohippurate. Being animal experiments, they have permitted us a more convenient medium for a very critical analysis of the pharmacodynamics of this form of therapy and a much more thorough check on the possible toxicologic effects to be anticipated in the clinical use of these combined materials. Moreover, they have served as a basis and justification for the initial combined use of penicillin and sodium p-aminohippurate in patients, reported elsewhere.<sup>2</sup>

We have found no evidence that the competitive tubular excretion of these two substances is on any basis other than physiologic. Therefore we have visualized the process as one involving a common transport system across the renal tubules in which the competition between penicillin and PAH for this common carrier is very likely one of mass action, and in which relative affinities of the two substrates for the same system play an undetermined rôle. It must be realized that the whole competitive process is a dynamic one which rapidly shifts as the plasma concentration of either component is varied within certain limits. All our evidence, functional and histomorphologic, substantiates this physiologic explanation which we have offered.

**Summary.** In these experiments it was shown that the combined intravenous administration of penicillin and sodium p-aminohippurate could be carried out continuously over a period of at least 48 hours without the occurrence of morphologic or functional changes directly attributable to these two compounds.

The intravenous administration of PAH to maintain plasma concentrations of about 30 mg./100 cc. invariably resulted in an increase in penicillin plasma concentration of from  $2\frac{1}{2}$  to 4 times the basal level, even though the concentration of penicillin was not varied. The stepwise increase in plasma PAH concentration above the level of 30 mg./100 cc. resulted in a further elevation of the penicillin plasma level although this was not a commensurate increase.

The effect of PAH in increasing the plasma concentration of penicillin was always reflected in a decrease in the renal clearance of penicillin.

Since PAH could not be demonstrated to be nephrotoxic by any method which we used, these findings support the concept that the effect of this compound is purely one of physiologic competition with penicillin for a common renal tubular excretory mechanism.

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## THE ANTISTAPHYLOCOCCAL ACTIVITY OF VARIOUS SULFONAMIDES

### WITH A METHOD FOR ROUTINE DETERMINATION OF CHEMOTHERAPEUTIC ACTIVITY\*

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THE antistaphylococcal activity of the sulfonamides in actual clinical use has not been compared *in vivo* on a quantitative basis so far. This is due perhaps to the difficulties often encountered in producing experimental infections with *Staphylococcus aureus* which are lethal for untreated animals but still sensitive to treatment with chemotherapeutic agents. Numerous authors used the intravenous,<sup>1,7,8,10,13</sup> subcutaneous,<sup>18</sup> or intraperitoneal<sup>5,6</sup> injection of heavy inocula of staphylococci for chemotherapeutic studies in mice. This heavy infection responded only to high doses of sulfonamides, and in many cases the effect was limited to a delay of the death of the animals. In other cases, a high ratio of the surviving animals was not cured but developed chronic infections.<sup>1,8</sup> Such results led to the opinion that the experimental staphylococcus infection is less sensitive to chemotherapeutic treatment than other coccic infections.<sup>8</sup>

The use of mucin for the intraperitoneal infection of staphylococci, recommended by Buttle,<sup>4</sup> improved the technique of infection and the results of the chemotherapeutic tests. This method apparently is now widely used.<sup>3,9,12,14,15,17</sup>

Different strains of staphylococcus tested in this laboratory proved to be highly virulent for mice if injected in a suspension of mucin. The infections produced with these strains were used for an extensive comparison of the antistaphylococcal activity of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine; the results of these experiments and the observations on infection and therapeutic activity are presented in this paper.

\* An abstract of this paper was presented at the 45th Meeting of the Society of American Bacteriologists, New York City, May 1944.

**Methods.** Seven strains of *Staph. aureus* have been tested. Strains No. 6339, 6340, 6342 and 6343, isolated from humans, were obtained from the American Type Culture Collection. *Staph.* 209 is the standard strain used by the Food and Drug Administration for the evaluation of disinfectants. *Staph.* Zorn was given to us by Dr. E. Bliss.\* *Staph.* B8 was isolated in our laboratory from a boil. All these strains possess the classical cultural and morphologic characteristics of *Staph. aureus*. Their toxin production was low on the media used.

For stock cultures, 6 hours growth on blood agar slants was prepared and kept in the ice-box. At the beginning of this investigation, fresh cultures were made once or twice weekly. Later, it was found that these strains keep their virulence for long periods (up to 1 year) if stored in the refrigerator; since then, stock cultures have been prepared once monthly. Attempts to obtain a consistent infection of mice with cultures in liquid or semisolid media were unsuccessful. Satisfactory results were obtained by the use of suspensions from agar slants. For the infection, a 15-hour culture on blood agar slants was prepared. The growth was suspended in 5 cc. broth, which was diluted to a constant turbidity. We used a turbidity giving 60% light transmission on the Fisher Electrophotometer, Mod. A.C., Filter A. Suspensions of the desired turbidity were diluted thereafter to  $10^{-6}$  in broth, and plate counts were made by means of a Quebec Colony counter. The counts of the suspensions so obtained were sufficiently uniform (200 to 700 cells in 1 cc. of a  $10^{-6}$  dilution). Mice were infected intra-abdominally with 1 cc. of the  $10^{-4}$  dilution in 5% mucin (without glucose). The  $10^{-4}$  mucin suspension contained an average of 50,000 cells.

Experiments were conducted on 40 to 100 mice, divided in groups of 5 to 10 mice for each dose and each preparation tested. Untreated control mice died within 24 hours, only occasionally (5 to 10%) 30 to 70 hours after infection. The behavior of the surviving treated animals was closely followed. The observation period was reduced from 60 to 90 days to 21 to 30 days when it appeared with certainty that deaths after the 14th day occurred only in a negligible number of mice. Succumbing untreated and treated animals were autopsied, and heart cultures were routinely made; often peritoneal smears were also taken. Surviving mice were killed at various intervals after infection, and organ cultures of lung, liver, spleen, kidney and heart were made on blood agar plates.

**Experimental.** 1. THE VIRULENCE FOR MICE OF STAPHYLOCOCCUS STRAINS IN MUCIN. Virulence titrations of the 7 strains used in our experiments are set forth in Table 1. All strains proved to be of satisfactory virulence.

TABLE 1.—MOUSE VIRULENCE OF *S. AUREUS* STRAINS  
(Intraperitoneal injection with mucin, 1 cc.)

No. of staphylococci injected	<i>Staph.</i> 6339	<i>Staph.</i> 6340	<i>Staph.</i> 6342	<i>Staph.</i> 6343	<i>Staph.</i> Zorn	<i>Staph.</i> 209	<i>Staph.</i> B8
Less than 10	7/12*	21/34		2/2	0/2	11/22	0/5
30-120	7/14	20/36	2/4	6/10	0/4	14/23	8/13
250-1200	14/23	51/76	5/5	3/5	4/10	17/30	22/25
2000-11,000	32/40	105/123	14/14	10/12	3/6	20/20	14/15
40,000-60,000	188/191	312/317		9/9	11/11	21/22	15/15

\* 7 mice died out of 12 injected.

Four of the 7 strains killed 80 to 100% of the infected animals if 2000 to 11,000 cells were injected. Three strains showed this rate of mortality with doses of 250 to 1200 staphylococci. All strains but

\* We are indebted to Dr. Bliss for this strain and for information on the technique used in her laboratory.

1 (Staph. Zorn) killed at least 50 to 60% of the infected animals if 100 staphylococci or less were given. It seems noteworthy that the virulence of an old laboratory strain, *e. g.*, Staph. 209, was not lower than that of a recently isolated strain, such as B8.

The virulence of these strains was largely dependent on the amount of mucin injected with the inoculum. It is shown in Table 2 that by decreasing the amount of mucin under 0.5 cc., a considerable drop in the incidence of fatal infection was observed.

TABLE 2.—INFLUENCE OF MUCIN VOLUME INJECTED ON THE VIRULENCE OF  
S. AUREUS 6340

(Intraperitoneal injection of 34,000 to 78,000 cells in 5% mucin)

Volume mucin:	0.1 cc.	0.25 cc.	0.5 cc.	0.75 cc.	1 cc.
No. of mice injected	3	6	6	3	10
No. of mice died	0	2	4	3	10

Injection with mucin results in spreading from the site of the infection, as reported for meningococcus by Miller and Castles.<sup>11</sup> Cultures of blood collected from the tail and cultures from heart and lungs showed that these organs were invaded  $\frac{1}{2}$  to 1 hour after intraperitoneal inoculation of 30,000 to 50,000 staphylococci in mucin; the growth became particularly abundant after 2 to 3 hours. The peripheral blood cultures showed occasionally isolated staphylococci during the first 10 hours after inoculation; but heavy growth was observed only after 18 to 24 hours, when the mice were already dying. This might have been due to the method in which only very small amounts of blood were used.

No spreading was observed if the same dose of 30,000 to 50,000 staphylococci was suspended in broth and injected intraperitoneally. Blood agar plate cultures from lungs and heart of mice taken at frequent intervals for the first 24 hours were negative. The organ cultures remained negative even after increasing the dose of infection to a count of 1 million.

The intra-abdominal route of infection with mucin proved to be the most reliable one. Experiments carried out with Staph. 6340 indicated that the subcutaneous as well as the intravenous injections were less satisfactory. Thirty million cells injected subcutaneously were always tolerated (80 mice). The MLD by subcutaneous injection consisted in 500 million cocci; by intravenous injection, at least 60 million cocci were required.

2. THERAPEUTIC EXPERIMENTS. The majority of the experiments by which the minimal active dose of the different sulfonamides was evaluated were done with Staph. 6340. This strain has been selected for routine determinations because its virulence was the most constant of the strains tested.

(a) *Results of Repeated Treatment.* Repeated treatment is commonly considered essential in testing of sulfonamides. This mode of treatment was used for the first comparison of antistaphylococcal activity of sulfonamides. In Table 3, the results are given. It appears that the minimal active dose—expressed as total dose per kg. body weight—for sulfadiazine is 0.175 gm.; for sulfathiazole, 0.350 gm.;

for sulfapyridine, 0.525 gm.; and for sulfanilamide, 1.75 gm. Surprisingly, the results with higher doses were less good. In order to clear this point, mice injected with mucin alone (without infection) were treated with sulfapyridine and sulfathiazole. It was found that the tolerance to these drugs is greatly decreased in mucin-treated animals. For instance, sulfathiazole killed mice previously injected with mucin in daily doses of 2 gm./kg., while normal mice tolerated daily doses of 10 to 15 gm./kg. It seems evident that mice treated repeatedly with high doses died of a combined toxic effect due to mucin, infection and drug. They showed staphylococci in their organs, indicating that death had occurred before the drug exerted its activity.

TABLE 3.—CHEMOTHERAPEUTIC ACTIVITY OF SULFONAMIDES IN THE *S. AUREUS* INFECTION WITH STRAIN 6340  
(Repeated oral treatment, 7 times)

Single dose in mg./20 gm. mouse	Sulfanilamide		Sulfathiazole		Sulfapyridine		Sulfadiazine	
	Mice	Surviv- ors	Mice	Surviv- ors	Mice	Surviv- ors	Mice	Surviv- ors
0.10	..	..	..	..	..	..	5	0
0.25	..	..	..	..	..	..	5	2
0.50	..	..	20	5	10	1	19	14
1.00	..	..	15	8	14	5	5	5
2.50	10	5	27	23	34	17	5	3
5.00	10	6	10	8	22	13	10	10
7.50	..	..	..	..	9	9	..	..
10.00	10	6	10	4	14	8	5	4
20.00	..	..	10	3	15	5	5	3

(b) *Results of Single Treatment.* In order to avoid the interference of toxicity, it was tried to reduce not only the dose but also the frequency of treatments. It has been found that a single treatment is sufficient to control the infection. This is shown in Table 4. The active doses by single treatment are: 0.050 gm./kg. for sulfadiazine, 0.250 for sulfathiazole, 0.375 for sulfapyridine. By this way of treatment, the phenomenon of "optimal dose" disappeared for sulfathiazole, sulfadiazine and sulfapyridine; the minimal active dose of sulfanilamide was not reached.

TABLE 4.—CHEMOTHERAPEUTIC ACTIVITY OF SULFONAMIDES IN THE *S. AUREUS* INFECTION WITH STRAIN 6340  
(Single oral treatment)

Single dose in mg./20 gm. mouse	Sulfanilamide		Sulfathiazole		Sulfapyridine		Sulfadiazine	
	Mice	Surviv- ors	Mice	Surviv- ors	Mice	Surviv- ors	Mice	Surviv- ors
(Controls)	317	5	..	..	..	..	..	..
0.10	..	..	..	..	..	..	5	0
0.25	..	..	..	..	..	..	5	1
0.50	..	..	..	..	..	..	44	17
1.00	..	..	..	..	..	..	55	36
2.50	..	..	25	2	25	0	25	24
5.00	10	1	48	21	20	6	18	18
7.50	..	..	40	26	44	29	..	..
10.00	40	8	10	8	15	11	..	..
20-30	20	5	10	8	10	9	..	..

The sensitivity of strains 209, B8, 6339 and 6343 to sulfonamide treatment was about the same as that of Staph. 6340: single oral

doses of 0.5 to 1 mg./20 gm. sulfadiazine protected the majority of the infected mice (Fig. 1).

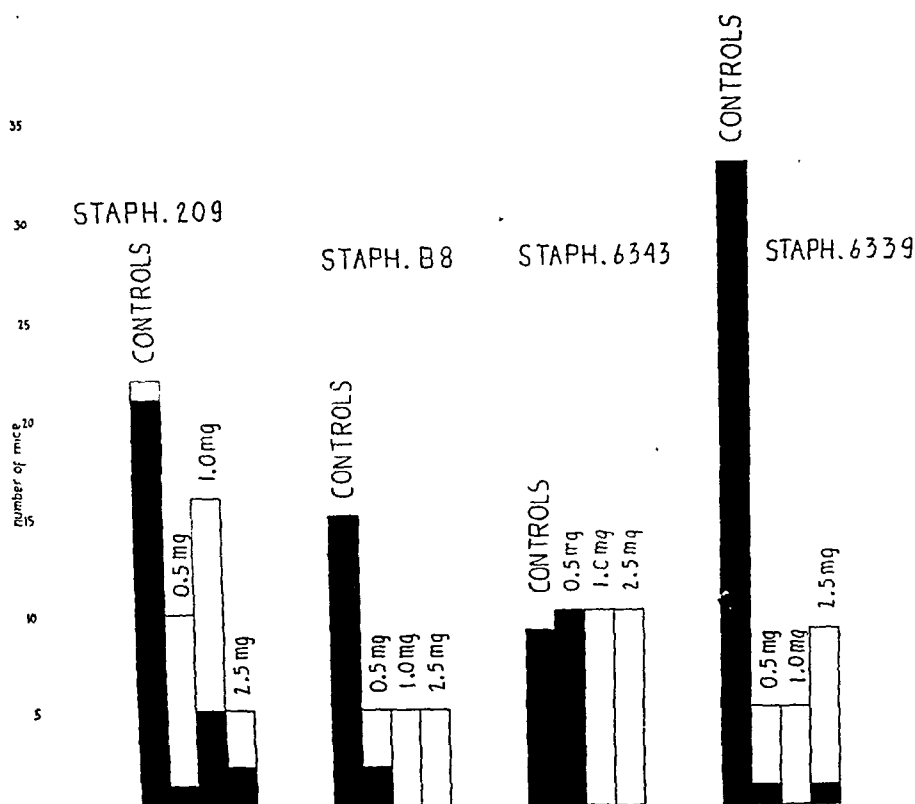


FIG. 1.—Single treatment with sulfadiazine.

(c) *Fate of the Survivors.* Mice surviving the infection after treatment have been sacrificed and autopsied at various intervals. A total number of 179 complete autopsies has been performed, and cultures of liver, spleen, lungs, kidneys, and heart on blood agar plate were made. The data obtained on survivors of infection with Staph. 6340 are given in Table 5.

TABLE 5.—ORGAN CULTURES OF MICE INFECTED WITH 1000-10,000 L.D. *S. AUREUS* 6340, TREATED WITH SULFONAMIDES

Kind of sulfonamide	Dose per 20 gm. mouse	No. survivors/ No. treated	4-13 days after infection organ cultures		22-120 days after infection organ cultures		Total organ cultures	
			+	-	+	-	+	-
Sulfanilamide	10 mg. single	8/15	..	4	1	2	1	12
	10 mg. repeated*	6/10	..	..	..	6	..	..
Sulfapyridine	5-10 mg. single	37/49	2	10	3	15	10	32
	2.5-10 mg. repeated	15/24	..	2	5	5	..	..
Sulfathiazole	2.5-10 mg. single	36/54	2	10	2	14	5	40
	0.5-10 mg. repeated	29/40	1	4	..	12	..	..
Sulfadiazine	0.5-2.5 mg. single	26/40	7	5	2	9	15	30
	5 mg. single	17/20	..	2	2	6	..	..
	0.5-1 mg. repeated	17/20	4	..	..	8	..	..

\* 7 treatments.



It appears that the majority (70%) of mice surviving the infection after treatment with sulfonamides is completely sterilized after 14 days. Mice sacrificed after longer intervals (60 to 120 days) showed a lower incidence of positive organ cultures than mice autopsied after 4 to 13 days; 84% of these animals were sterilized. The difference found in the number of mice sterilized with the various sulfonamides tested are not considered to be statistically significant.

(d) *Activity and Blood Concentration.* In order to relate the therapeutic results obtained with the concentrations reached in the blood, the absorption following single oral administration of the drugs was determined. The drugs were suspended in 1 cc. of a 5% gum acacia solution and administered to a group of 5 to 7 mice. Mice under ether anesthesia were bled from the external jugular vein at various intervals after administration. The free and conjugated sulfonamide content in the blood was determined according to Bratton and Marshall.<sup>2</sup> The results obtained show that in the therapeutic dose ranges used, sulfadiazine results in a higher and more prolonged blood concentration than the other sulfonamides tested (Table 6). The results on absorption correspond closely to those reported by Schmidt and Sesler.<sup>16</sup>

TABLE 6.—ABSORPTION OF SULFONAMIDES AFTER SINGLE ORAL ADMINISTRATION

Drug	Dose mg. per 20gm. mouse	No. of mice	Blood concentration (total) in mg. % after hours						
			½	1½	2½	3½	4½	6	7-8
Sulfanilamide	0.5	5	2.0	1.5	0.8	0.8	0.5		
	1.0	13	2.5	2.0	1.5	0.7	0.3	0.5	Tr.
	2.5	18	7.0	5.0	4.0	2.8	1.2	0.5	
	5.0	8	9.5	10.0	5.0	4.5	3.5	2.0	0.5
Sulfapyridine	0.5	4	4.0	2.0	1.0	0.25			
	1.0	4	4.5	4.0	2.0	3.5			
	2.5	11	5.7	7.0	5.7	5.0	4.5	3.8	
	5.0	9	9.0	12.0	9.0	9.0	8.0	5.5	3.0
Sulfathiazole	0.5	13	1.75	0.5	0.4	0.5	Tr.		
	1.0	5	4.0	1.5	0.5	0.5	Tr.		
	2.5	18	7.5	3.0	1.4	1.0	0.5		
	5.0	6	11.0	9.0	7.0	2.5	2.5	2.5	
Sulfadiazine	0.5	13	5.5	6.0	4.3	5.1	5.5		
	1.0	8	8.5	8.0	8.2	7.5			
	2.5	6	11.0	11.0	8.0	8.0	8.0	7.0	
	5.0	14	15.0	18.0	10.0	10.0	12.0	..	10.0

**Discussion.** The experiments described in this paper show that sulfonamides have a very definite activity on the *Staph. aureus* infection, in the following order: sulfanilamide < sulfapyridine < sulfathiazole < sulfadiazine. These results are in agreement with those of Barlow and Homburger,<sup>1</sup> and Rake and McKee,<sup>14</sup> who found a better activity for sulfathiazole than for sulfapyridine. The effective doses reported here gave (50%) protection against the lethal effect of the infection and brought about complete sterilization in the majority of survivors, as shown by autopsies and organ cultures.

The lowered resistance caused by the use of mucin as an aid for infection was found to decrease also the tolerance of mice to the drug. This explains the phenomenon of the unsatisfactory activity of high doses (10 to 20 mg.) if given repeatedly. Less favorable results of other investigators who used such dosages might be due to this inter-

ference of toxicity with the therapeutic effect. These difficulties have been overcome by the use of single treatment which presented other advantages too. The use of repeated treatment tended to overdose the drug and made the evaluation of the minimal active dose less reliable than that of 1 single treatment. This point is illustrated by Table 7.

TABLE 7.—AVERAGE ACTIVE DOSES OF SULFONAMIDES IN THE *S. AUREUS* INFECTION OF MICE  
(Oral doses in gm./kg.)

Drug	Single treatment (A)	Repeated treatment		Ratio C/A
		Single dose (B)	Total dose (C)	
Sulfanilamide . . .	0.375	0.250	1.750	
Sulfapyridine . . .	0.375	0.075	0.525	1.4
Sulfathiazole . . .	0.250	0.050	0.350	1.4
Sulfadiazine . . .	0.050	0.025	0.175	3.5

It is evident that in the case of sulfapyridine and sulfathiazole the effective doses for single treatment correspond closely to the total required for repeated treatment with small doses. In the case of treatment with the more active sulfadiazine, the minimal active dose for repeated treatment is 3.5 times higher than required for single treatment. We should like to point out that lower doses given repeatedly, such as 0.0125 and 0.005 gm./kg., were inactive, even though the total amount given exceeded the effective dose by single treatment (0.05 gm./kg.). This would indicate that in order to obtain protection, a sufficiently high initial dose is necessary for the repeated treatment. Altogether, it seems that the treatment with single doses, besides its technical advantages, gives simpler and more clear-cut results.

It is probably not coincidental that sulfadiazine, which showed the highest activity, was better absorbed and gave a blood level of longer duration than the other drugs. No relationship could be found, however, between activity and blood concentration of sulfanilamide, sulfathiazole and sulfapyridine. In fact, the less active sulfapyridine was found to be better absorbed than sulfathiazole.

**Summary.** 1. The virulence of intra-abdominally injected staphylococci for mice and the influence of mucin on this infection was studied. A method of infection is described which was found suitable for routine determinations of chemotherapeutic activity.

2. The evaluation of sulfonamides administered orally showed that sulfadiazine is about 5 times more active than sulfathiazole. Sulfathiazole is about  $1\frac{1}{2}$  times more active than sulfapyridine. Sulfanilamide itself showed a low antistaphylococcal activity.

3. Sulfadiazine, sulfapyridine and sulfathiazole were active even if only 1 single treatment was given shortly before intra-abdominal infection. This mode of administration gave particularly clear-cut results.

4. Autopsies and organ cultures of treated mice showed complete sterilization in the majority of survivors after 14 days.

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## PERSISTENCE OF PNEUMOCOCCI IN SULFONAMIDE TREATED CASES OF PNEUMONIA

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IN a series of papers beginning in 1938 Frisch<sup>2-4</sup> has described the morphologic features and some of the quantitative aspects of the pneumococci found in stained smears of sputum from cases of pneumonia. He has also described the changes which result from treatment with specific antisera and with sulfonamide drugs and has indicated their prognostic significance as well as their importance in the control of therapy. The studies which are reported, in part, in this paper were undertaken during the fall and winter of 1941-1942 for the purpose of determining the changes in the bacterial flora of the sputum and pharynx in cases of pneumococcal pneumonia during and after sulfonamide therapy.\* An attempt was made to quantitate

\* The Senior Author, having been called to military service before this work was completed, it was not possible to complete the work until now. Nevertheless, as the material is still timely, we believe that it represents a useful contribution.

roughly these changes, not only in the pneumococci but also in the relative numbers of the other common respiratory pathogens. In addition to direct morphologic studies similar to those carried out by Frisch, cultural methods were applied to sputum and throat swabbings, and mouse inoculation of sputums and throat cultures were used in each instance.

The present report deals with the results of these studies as they pertain to the persistence, during and after treatment with sulfonamides, of the pneumococci originally present, the appearance of additional types of pneumococci and the fate of these new strains. Earlier studies on the persistence of pneumococci in cases of pneumonia have been reviewed by Finland<sup>1a</sup> and by Harris<sup>6</sup> and the latter reported similar studies in patients treated with sulfapyridine and sulfathiazole. The data bearing on the significance of the finding of various types of pneumococci in patients with pneumonia are reviewed elsewhere.<sup>1b</sup>

**Materials and Methods.** *Selection of Cases.* The patients chosen for this study were all adults admitted to the medical wards at the Boston City Hospital between the end of September 1941 and the middle of April 1942. They ranged in age between 15 and 64 years and 8 of them were over 50. All of them were acutely ill with pneumonia and had fever, cough and sputum at the time of the first examination and pneumococci were identified in the sputum at that time. There was definite lobar pneumonia by physical examination and by Roentgen ray in all but 5 of the cases. In these 5 cases, there was atypical consolidation that was bilateral, but in 2 of them there was lobar consolidation of 1 lobe in addition. There were 43 patients in all and 3 of them were observed in 2 attacks.

*Sulfonamide Therapy.* Each of the patients was treated with sulfonamide drugs. Sulfathiazole was used alone in 35 cases, sulfadiazine alone in 4 cases and both of these drugs were used in succession in 6 cases. One of the 3 patients who was observed during 2 attacks received no sulfonamide during the second attack. Treatment was begun in these patients between the 1st and the 8th day after the onset of symptoms of pneumonia. In 31 instances treatment was begun on or before the 3rd day. In 9 cases it was begun on the 4th or 5th day. The average duration of the disease at the time when the treatment was begun was 2.8 days. The usual dosage of sulfonamides was used, namely, 4 gm. for the initial dose followed by 1 gm. every 4 hours. Treatment was continued for 3 days or less in 4 cases, for 4 to 6 days in 18 cases, 7 to 10 days in 17 cases and 15 or more days in 6 cases. The average duration of treatment was 7.6 days. The average dose was 47 gm., about one-half of the patients receiving between 30 and 50 gm. The average blood sulfathiazole level during therapy in 80% of the cases was between 3 and 7 mg. per 100 cc. of the free drug. In 5 instances, high levels were associated with vomiting and nitrogen retention. Specific antipneumococcus serums were used in 3 cases (Nos. 24, 27 and 28).

*Bacteriologic Studies.\** Blood cultures were made before treatment in every instance and at frequent intervals after treatment when indicated. Positive cultures were obtained in 8 of the patients, including 4 of Type 1, 3 of Type 7 and 1 of Type 4 pneumococcus.

Sputums were subjected to the following studies: (1) Direct examination for pneumococci with specific antipneumococcus serums by the Neufeld method. (2) Gram stain preparation. (3) Wright stain preparation examined by the method of Frisch. (4) The sputum was homogenized and a 2 mm. loopful streaked thoroughly on the surface of a blood agar plate containing

\* Para-aminobenzoic acid, 5 mg. per 100 cc. was incorporated in all media used in this study.

10% defibrinated horse blood. Characteristic colonies were picked and identified and a rough estimation was made of the relative numbers of the different kinds of organisms. (5) Some of the sputum was also inoculated into mice and the peritoneal exudate was examined at suitable intervals by the Neufeld method and cultures of the heart's blood were made and the pneumococci typed when the mouse died or was sacrificed.

Throat cultures were made in some instances at the same time as the sputum and in every instance where sputum was not obtainable. A cotton swab was rubbed against both fauces and against the posterior pharyngeal wall and placed into a tube of nutrient broth containing 1% defibrinated rabbit blood. Some of the broth was mixed thoroughly and streaked directly on the surface of a blood agar plate. The broth was allowed to incubate for 4 to 8 hours until a uniform growth appeared. At that time some of the culture was examined by the Neufeld method and a portion was inoculated, on blood agar plates and intraperitoneally in mice and the peritoneal exudate of the latter examined by the Neufeld method at suitable intervals. The heart's blood of such mice was also cultured when the animals died or were sacrificed.

The Neufeld preparation made directly from the sputum was studied both for the various types of pneumococci and for the numbers of each type. In the Gram and Wright stain preparations similar counts were made of characteristic lancet-shaped diplococci. In the Wright stain preparation observations were also made of clumping and phagocytosis of diplococci and also of reticulation as noted by Frisch.<sup>2</sup>

The direct surface cultures were observed for the relative numbers of the common respiratory pathogens, namely, pneumococci, hemolytic and green-producing streptococci, *Staphylococcus aureus* and *Hemophilus influenzae*. These various organisms other than the pneumococci were identified only by their colony characteristics and their morphologic appearance in stain smears and the staphylococci were also tested for coagulase activity.

The throat cultures were studied mainly with the idea of observing the persistence of pneumococci. The pneumococci were identified by subjecting the direct cultures, the peritoneal exudate of mice or the characteristic colonies picked from the blood agar plate to the action of type-specific antisera (Neufeld). Doubtful colonies were subcultured and tested for bile solubility. Sensitivity of the strains to sulfonamides was tested by essentially the same method as was used in a previous study in this laboratory.<sup>7</sup>

Sputums and throat cultures were thus obtained before the first dose of sulfonamide and at suitable intervals during and after treatment. A total of 244 sputums were studied in the 46 cases, and, in addition, 90 throat cultures were made in 35 of the cases making an average of more than 7 specimens studied in each attack. The average hospital stay for each attack was 18 days, but the patients were asked to return after discharge from the hospital for follow-up studies. The last sputum or throat culture was made in 15 cases on or before the 15th day; in 14 cases between the 15th and 30th day; in 14 cases between the 31st and 60th day; 3 cases were observed for longer periods. The average time between the first and the last observation was 31 days. This period is exclusive of the interval between the recurrences in 3 of the patients.

**Results.** In this paper, only the results of the findings of pneumococci in this series of cases are being presented. The types of pneumococci found before treatment was begun and data concerning the persistence of these pneumococci are given in Table 1. In addition, the relevant findings concerning the pneumonia and the sulfonamide therapy are summarized for each case in this table. A total of 51 strains were isolated before treatment in the 46 attacks which occurred in the 43 patients studied. Of these, 34 strains were of the types commonly associated with primary lobar pneumonia, namely, Types 1,

TABLE 1.—FATE OF PNEUMOCOCCI FOUND IN SPUTUM AT THE TIME SULFONAMIDE THERAPY WAS STARTED

Case No.	B.C.	Lobes	Chemotherapy				Pneumococci		Day last test		Complications, clinical response, etc.
			Drug	Begun	Grams	Days	Type	Days			
1	0	Ll	T4	2	29	6	8	10	10	C1	
2	0	Rl	T7 D8	3	35	6	1	48	48	C2	
							3	1			
3	0	Ll	T13	2	16	2½	1	2	12	C1	
4	0	B	T3	2	32	4½	11	3	6	C1; chronic bronchitis	
5	0	Ll	T4	1	35	8	27	1	41	C2; chronic bronchitis	
							24	41*			
6	0	Ll	T6	5	25	3½	25	7	179	C2; pn. (?) 9 yrs. before	
6R	0	Rm	T7	2	25	3	19	10	10	C1; recurrence after 5½ mos.	
7	0	Ll	T7	2	25	3	8	118	118	C1; bronchiectasis; sinusitis	
8	0	Ruml	T6	5	57	10	2	2	9	D16; alc.; uremia	
9	1	Ll	T4	7	54	8	1	2	23	C1; alc.; sinusitis	
10	0	Ll	T5	3	50	8	1	3	177	C2; frequent colds	
							6	1			
11	0	Ru	T5	2	25	3½	2	2	77	C2; pn. several times	
11R	0	Rl	T3	2	36	5½	12	3	11	C1; recurrence after 2 mos.	
							8	1		? bronchiectasis	
12	0	Ll	T4	3	45	7	8	19	19	L2-5; pn. (14) and pn. (2) 4 and 2 yrs. before; chronic bronchitis	
13	0	Rml	T3	4	44	7	7	4	8	C2; alc.	
14	7	Ll	T6 D	10	54	8	7	3	10	D10; meningitis (7); sinusitis, Staph. aureus and Strep. hem.	
15	0	Rml	T5	3	32	5	1	11*	11	C2	
16	0	Ru	T	2	7	1	2	9	22	L3; pn. (1) 4 yrs. before	
17	0	Rm	D9	1	36	6	1	2	8	C2; otitis	
18	0	Rul	T3	4	40	6	2	8*	8	C3	
19	0	B	D9	6	39	8	3	237*	237	L2-3; chronic bronchitis	
19R	0	B	D9	5	28	5	3	196*	196	C1; recurrence after 6 wks.	
20	1	Rum	T9	2	43	7	1	1	33	L2-4; pn. (4) 4 yrs. before	
21	4	Ru	T12	6	10	1	4	50*	50	C1; relapses—fever 26 days; azotemia	
22	0	Rml	T4	1	28	4	14	3	83	C2	
23	0	B Ll	T10 D11	1	43	6	3	1	17	C2; oliguria; azotemia; drug fever; chronic bronchitis	
24	0	B	T9 D20	4	48	8	9	9	9	D9; Type 9 antiserum 8th day	
25	0	Ruml	T4	7	36	5	4	1	10	L1-2; pn. (6) 1 yr. before; alc. D.T.	
26	0	Rl	T4	1	42	7	3	2	8	L3	
27	0	Llu	T3	1	100	16	29	5	25	L18; post-traumatic; Type 29 antiserum 3rd day; sterile pleural effusion	
28	7	Ll	T3	2	98	16	7	5	57	L13; Type 7 antiserum 1st day; alc.; sterile effusion	
29	1	Rml	T3 D	3	162	26	1	87*	87	Empyema, rib resection	
30	1	Ll	T6	3	87	19	1	1	26	C1; sterile pleural effusion	
31	0	R2	T3	5	42	6	7	1	39	C2	
32	0	R2	T5	2	25	5	5	36	100	C2; persistent "colds"	
33	0	L2	T3	2	33	5	7	1	3	C2; pn. 12 yrs. before	
34	0	L2	T5	2	61	10	1	18*	32	C2; pn. 2 yrs. before; sterile pleural effusion	
35	0	Ru	D	3	52	8	2	1	54	C2; pn. (7) 3 yrs. before and pn. (1) 1 yr. before; pn. 8 other times; bronchiectasis	
							33	2			
36	0	Rml Ll	T5	1	48	8	3	1	16	C1; alc.; chronic bronchitis	
37	0	Lul	T11	4	57	9	2	28*	28	C2; chronic bronchitis; sinusitis; pn. 10 yrs. before; otitis	
38	0	Rul	T4	1	32	4½	1	8	20	C2; pn. in childhood	
39	0	L2	T6	1	30	4½	5	2	7	C2	
40	7	Rml	T5 D11	5	121	20	7	29*	34	Empyema; drug fever and rash	
41	0	L2	T5	2	44	8	1	3	27	L1-3	
42	0	L2	T3	2	47	7	7	21*	21	L2-4	
43	0	L2	T4	2	98	18	1	1	13	C2; empyema	

ABBREVIATIONS AND EXPLANATIONS: Under "Case No.": R = recurrent infection; B.C. = blood culture; 0 = no growth, numeral = type of pneumococcus found in positive B.C. Under "Lobes": L = left; R = right; u = upper; l = lower; m = middle; B = diffuse bronchopneumonia. Under "Drug": T = sulfathiazole; D = sulfadiazine; the numbers represent the average blood levels of free drug in mg. % to the nearest whole number. Under "Begun": numbers represent days after onset of the disease. "Days" Under "Chemotherapy," "Pneumococci" and "Day Last Test": the numbers represent days after sulfonamide therapy was started, the last of these being the day when the last specimen was obtained. Under "Clinical Response, Etc.": C = crisis; L = lysis; D = died; the number after these letters represent the day after drug therapy was started. pn. = past history of pneumonia, the number in parenthesis being the type when known; Alc. = alcoholism; D.T. = delirium tremens.

\* One or more specimens prior to the last one were negative for the same type.

2, 5, 7 and 8; 6 strains were Type 3; 11 strains were either Type 6 or of the so-called "higher" types.

There were 5 cases in which 2 types were isolated before treatment was begun: Types 1 and 3 were found in Case 2, Types 27 and 24 in Case 5, Types 1 and 6 in Case 10, Types 2 and 33 in Case 35 and Types 12 and 8 during the recurrence in Case 11. Except in Case 5, therefore, one of the common types was found in conjunction with one of the "higher" types or with one of the types commonly found in carriers (namely, Types 3 and 6). In 1 of the cases observed during 2 attacks the Type 3 pneumococcus was found before treatment in each attack.

*Persistence of the Pneumococci Found Before Treatment.* Of the 51 strains, 36 could no longer be found in the last sputum or throat culture. The last specimen in which these 36 strains were found was obtained on the 1st day of treatment in 13 instances on the 2nd or 3rd day in 14, on the 4th to 7th day in 4 and on the 8th day or later in the remaining 5 strains. In 2 of the latter, several specimens failed to yield pneumococci but these reappeared toward the end of the period of observation. The average time elapsed from the onset of treatment to the time when these strains were last found was 4.7 days, and 27 of these 36 strains of pneumococci were last found on or before the 3rd day. Thirty of these 36 strains (83.3%) had disappeared from sputum or throat cultures before the course of sulfonamide therapy was completed. The average period of observation of these cases was 41 days.

The 15 remaining strains\* persisted throughout the period of observation which averaged 60 days. The last sputum or throat culture was studied during the 2nd week in 4 cases, during the 3rd or 4th week in 4 others, during the 2nd month in 4 cases and from 5 to 8 months after treatment in the remaining 3 cases. In 9 instances these strains were found intermittently throughout the period of observation, that is, each of them could not be found in one or more specimens studied before the last one was obtained. Pneumococci tended to persist when treatment was begun after the 2nd day of illness although some cleared rapidly even in cases treated after 7 days.

*Appearance of Additional Strains of Pneumococci During or After Therapy.* In addition to the strains of pneumococci identified before treatment was begun, pneumococci of different types appeared after treatment was begun in 17 patients including Case 19 in which a second and different type appeared during each of 2 attacks. The types of these strains and the time of their first and last appearance are shown in Table 2. It is of interest that only 1 of these new strains was of any of the common types, other than Type 3, which are usually associated with primary pneumococcal pneumonia. The isolated instance was that of a Type 1 pneumococcus, which was found only in the last specimen studied in Case 28. A Type 4 pneumococcus was found on the 2nd day of therapy of the recurrence in Case 19. Of the

\* The Type 3 pneumococcus in Case 19 is counted twice since it was found before treatment in each of 2 attacks.

remainder, 4 were Type 3 strains and 20 were of the "higher" types. In Case 5 there were 4 types identified in addition to the 2 types which were originally present before sulfonamide therapy was begun and in Case 28, 4 new types of pneumococci made their appearance after treatment was begun, in addition to the Type 7 which was originally present. In 3 other cases, 2 new types were first found after the onset of therapy and in the remaining cases only 1 new strain was identified in addition to those originally identified before the onset of therapy.

TABLE 2.—APPEARANCE AND FATE OF PNEUMOCOCCI FOUND FOR THE FIRST TIME AFTER SULFONAMIDE THERAPY WAS STARTED

Case No.	Sulfonamide treatment (days)	Pneumococcus type	Days after chemotherapy begun		
			First appeared*	Last found	Agglutinins demonstrated
1 . . . . .	6	17	5	5	None
2 . . . . .	6	18A	48	48	4
5 . . . . .	8	13	2	13	1
		20	4	41†	None
		3	4	8	1
		19	25	41	None
7 . . . . .	3	17	118	118	None
10 . . . . .	8	14	149	177	None
		15	149	177	None
16 . . . . .	1	9	22	22	4
19 . . . . .	8	29	3	4	1
19R . . . . .	5	4	2	2	21
22 . . . . .	4	28	32	83	None
		24	54	54	None
26 . . . . .	7	15	4	4	40
28 . . . . .	16	21	10	10	None
		3	43	43	None
		23	43	43	None
		1	57	57	None
29 . . . . .	26	27	87	87	35
32 . . . . .	5	28	20	100	None
34 . . . . .	10	3	2	2	None
35 . . . . .	8	24	14	54	None
41 . . . . .	8	20	8	27	None
43 . . . . .	18	3	2	2	None
		13	3	3	None

For relevant data concerning these cases see Table 1. Pneumococcus type present when treatment of a recurrent infection was started are not listed here but are given in the previous table. Agglutinins listed are for the corresponding types; the numbers represent days after treatment when antibodies were first demonstrated.

\* 14 of these 26 strains were first found while the patient was still receiving sulfonamides.

† Several sputums were interspersed through the course of the illness from which this type was not recovered.

Altogether, therefore, there were 26 additional strains found in these 17 patients; 14 of these strains appeared in 9 patients while sulfonamide therapy was still being given. The remaining 12 strains were first observed in 8 cases after the sulfonamide therapy had already been discontinued. Nine of the former strains and 7 of the latter were found only in a single sputum or throat culture and in 5 instances that was the last specimen studied. Of the 10 strains which were found more than once, 3 persisted for only 1 to 11 days and the remain-



ing 7 were still present in the last specimen studied which was obtained from 16 to 80 days after these strains first appeared.

A summary of the occurrence of the different types of pneumococci both those present before treatment and those which made their first appearance after treatment was begun, is given in Table 3. A total of 77 strains of pneumococci were identified in the 46 cases studied. A single type of pneumococcus was obtained during 28 of these attacks; 2 different types were obtained in 11 cases; 3 types in 4 cases and 4, 5 and 6 types were obtained in 1 case each.

TABLE 3.—DISTRIBUTION OF TYPES ACCORDING TO THEIR APPEARANCE AND FATE IN RELATION TO SULFONAMIDE THERAPY

Types	Number of strains present before sulfonamide therapy		Number of strains which appeared after sulfonamides were begun		Total
	Absent from last specimen	Present in last specimen	Absent from last specimen	Present in last specimen	
1, 2, 5, 7, 8 . . .	24	10	1	1	36
3 . . . . .	4	2	4	0	10
Others . . . . .	8	3	8	12	31
All . . . . .	36*	15	13†	13‡	77

\* 30 of these strains were already absent from the sputum or throat culture before sulfonamide therapy was ended and the other 6 were still present after chemotherapy had been discontinued.

† 9 of these strains disappeared during sulfonamide therapy and 4 were still present after chemotherapy was stopped.

‡ 4 of these strains, including a Type 1 strain, were found only in the last specimen.

*Recognition of Pneumococci During and After Sulfonamide Therapy.* Throughout this study there was no difficulty in recognizing pneumococci and identifying their types irrespective of whether they were found before treatment was begun, during therapy or after the sulfonamides had been discontinued. In almost every instance in which sputum was available the pneumococcus types were identified directly in the sputum by the Neufeld method. In every instance characteristic colonies were observed on the surface of blood agar plates and the organisms preserved their morphologic and cultural characteristics and their virulence for mice. All of the strains present in the peritoneal exudate or in the heart's blood of mice were easily identified by the Neufeld method.

*Clinical Response to Treatment.* There were 3 deaths in this series. In 1 of these cases (No. 8) blood cultures were negative; death was associated with uremia, and the Type 2 pneumococcus originally present in the sputum could not be found after the first 2 days of sulfonamide therapy. In Case 14, the Type 7 pneumococcus was obtained from blood cultures taken before and 12 hours after treatment was begun, but not thereafter; it was found in the sputum only during the first 3 days but it was recovered from the purulent meningeal exudate at autopsy. In Case 24, blood cultures were negative but the Type 9 pneumococcus persisted in the sputum up to the day of death. In the latter case, specific antipneumococcus serum was given on the day before death.

Among the recovered cases, 31 were essentially afebrile and free of acute symptoms within 48 hours after the first dose of sulfonamide, while in 8 others some fever and acute symptoms persisted for 3 to 5 days. In 4 cases, persistent fever was associated with pleural effusions, 2 of which were sterile and the other 2 infected. In 1 other case of empyema and in 2 additional cases with sterile pleural effusions fever recurred after an apparently critical improvement associated with drop in temperature to normal which occurred within 48 hours of the beginning of treatment. Of the 36 strains present before treatment in the 31 cases in which recovery took place within 48 hours, 22 (61%) persisted only for 3 days or less, whereas 5 of the 8 strains originally found in the patients who had fever for 3 to 5 days were found for 8 days or longer after treatment was begun. The cases with complications will be considered later.

*Bacteriemic Cases.* There were 8 patients in whom positive blood cultures were obtained before sulfonamide therapy was started. In 5 cases pneumococci of the type found in the blood could not be found in the sputum or throat cultures after the 3rd day. In the other 3 cases the same type was found in the sputum or throat cultures throughout most or all of the period of observation; 2 of the latter cases had empyema and the third (Case 21) had azotemia during sulfonamide therapy and a relapse of fever after 26 days.

*Complications of the Pneumonia and Their Effect on the Persistence of Pneumococci.* Empyema occurred as a complication in 3 cases. In 1 of them, Case 29, Type 1 pneumococci were found intermittently throughout the 87 days of observation and a Type 27 pneumococcus appeared for the first time in the last sputum examined. In a second case, No. 40, the Type 7 pneumococcus was found in all but 1 of the specimens obtained up to the 29th day but not thereafter. In Case 43, the Type 1 pneumococcus was found in the sputum only on the 1st day of treatment although it was recovered during the following 12 days from cultures of the pleural fluid. Types 3 and 13 pneumococci were each found on 1 occasion on the 2nd and 3rd days respectively. In Case 14, meningitis occurred terminally and Type 7 pneumococci were obtained from cultures of the meninges but this organism could not be obtained from the sputum later than 36 hours after sulfonamide therapy was started. Blood cultures in this case were positive before treatment was begun and 12 hours after the first dose but were negative thereafter. Bilateral catarrhal otitis media occurred in Case 17 and in Case 37, but pneumococci persisted in the sputum only in the latter. Extension of the pulmonary process occurred early in the course of sulfonamide therapy in Case 25 and Case 27 but pneumococci could not be recovered after the 1st day of treatment in the former and after the 5th day in the latter.

*Previous History of Pneumonia.* Such a history was obtained from the patient or from the hospital records in 16 cases. In 11 of them there was no information concerning the bacteriology of the previous attacks. In 5 of the patients, however, the previous attacks were associated with type-specific pneumococci and they included 2 patients

in which there were 2 previous attacks of pneumococcal pneumonia. In each of these 7 previous attacks the type of pneumococcus was different from the one found in the present series. Of the 3 cases which were observed during 2 attacks in the course of this study, 1, Case 19, had a Type 3 pneumococcus before treatment on each occasion, but Type 29 was found in addition on the 3rd day of the first attack, and Type 4 was obtained on the 2nd day of the recurrence which began after an interval of 6 weeks. The interval between the initial observed attack and the recurrence was  $5\frac{1}{2}$  months in Case 6 and 2 months in Case 11. In these 2 patients different types of pneumococci were obtained in each of the attacks. The pneumococci found in this group of cases behaved in about the same manner as in the other cases. More than half of the 21 strains from these cases could be found for only 1 to 3 days while the others persisted for varying periods.

*Effect of Chronic Respiratory Infections.* A history of chronic bronchitis was obtained in 11 cases, and 3 other patients had chronic or frequently recurring infections of the upper respiratory tract. In this group of cases there was considerable variation in the persistence of pneumococci. In some of them the pneumococci found in the sputum before treatment cleared rapidly, in others they persisted for a variable period and then could no longer be found, and there were still others in which the pneumococci were recovered throughout the period of observation. In 7 of these cases there were multiple types of pneumococci. The new types which appeared during or after sulfonamide therapy showed similar variations with respect to the time during which they could be recovered.

*Immunologic Findings.* Antibodies were demonstrated for 1 of the types of pneumococci originally found in the sputum in all but 2 cases, namely Case 19 in which Type 3 was found and Case 32 in which there was a Type 5 pneumococcus. In only 1 of the cases in which 2 or more types were found before treatment were agglutinins found against more than 1 of these types; in Case 2 agglutinins for the Type 3 pneumococcus were found in the serum obtained before treatment and Type 1 antibodies appeared later. In the remaining cases antibodies developed against only one of the types originally found in the sputum. In Case 5 agglutinins developed for Type 27 but not for Type 24; in Case 10 antibodies were demonstrated for Type 1 but not for Type 6. In Case 11 agglutinins for Type 2 pneumococci developed during the first attack but none could be demonstrated either for the Type 8 or the Type 12 pneumococci which were found before the treatment of the second attack and in Case 35 antibodies developed during the course of treatment against Type 2 but none could be found against Type 33 in any of the serums tested.

As to the types which appeared after treatment was begun (see Table 2) antibodies for them could not be demonstrated in any of the serums in most instances. Agglutinins were found, however, against 8 of the strains, but in 6 instances these antibodies were already present in blood which was obtained before the homologous type first made its appearance.

*Susceptibility of Strains to Sulfonamides.* A total of 76 pure cultures from isolated colonies of 43 strains of pneumococci obtained from 26 patients were tested for their sensitivity and for their susceptibility to the action of sulfathiazole and sulfadiazine. In 22 instances the strain was tested from only a single isolation which usually was the one made from sputum obtained before treatment was started. The remaining 21 strains were each freshly isolated on 2 to 6 different occasions during and after sulfonamide therapy. The first isolation of each strain was usually made before treatment was begun. The interval between the first and last isolations of the 21 strains of which there were multiple cultures varied from 2 to 55 days and averaged 14 days. The cultures were tested in large batches and all of those obtained from the same case were tested at the same time.

The growth of all of the cultures of the various strains was inhibited by lower concentrations of sulfathiazole than of sulfadiazine in parallel tests. The inoculum was approximately 10,000 diplococci per cc. in each instance. Growth in rabbit blood broth was completely inhibited by sulfathiazole in concentration of 5 mg. per 100 cc. in 18 of the cultures and in 2.5 mg. in 53 cultures. In 3 instances, there was complete inhibition of growth with 1 mg. per 100 cc. and 2 others required 10 mg. to bring about this result. For sulfadiazine, a concentration of 10 mg. per 100 cc. was required for complete or nearly complete inhibition of 6 strains; 5 mg. for 52 strains; 2.5 mg. for 17 strains; 1 mg. for 1 of the strains. These concentrations were sufficient to prevent visible growth from occurring in the broth cultures and only occasional colonies grew out in some of them when transfers were made after 48 hours to a blood agar plate containing para-aminobenzoic acid. Although these differences were noted among the various strains, no significant differences could be demonstrated in the resistance of any one strain which was isolated on more than one occasion.

*Discussion.* After sulfapyridine and the other effective sulfanilamide derivatives came into general use, the impression became prevalent that it is difficult or impossible to culture and to type pneumococci from cases of pneumonia which are under treatment with these drugs. Part of the purpose of the present study was to determine whether this was due to the actual disappearance of the pneumococci during treatment or whether it was necessary to use more extensive cultural methods or mouse inoculation in order to find them. In general, it was found that when pneumococci were present, they usually could be identified in the sputum even during the course of sulfonamide therapy. Only in occasional specimens were pneumococci obtained from cultures or after mouse inoculation when they could not be found by careful search of the sputum in a Neufeld preparation. In cases which responded favorably, to be sure, pneumococci were often present in very small numbers during the sulfonamide therapy and some of the organisms showed the morphologic changes described by Frisch.<sup>2</sup>

The data presented indicate first of all that there are considerable variations in the persistence of pneumococci in cases of pneumonia treated with sulfonamides just as had previously been shown in cases

not treated with these drugs. In a large proportion of sulfonamide treated cases, however, it was not possible to find the pneumococci after the 2nd day of adequate therapy. As far as could be judged from the small amount of data available, the pneumococci tended to persist longer in those cases in which the clinical response to treatment was delayed than in those in which the fever and the acute symptoms subsided in less than 48 hours after the sulfonamides were started.

In general, pneumococci tended to persist longer in cases with purulent complications, and in those in which there was a history of chronic respiratory infections. In the latter cases additional types were recovered more frequently during and after sulfonamide therapy. It is possible that minor unrecognized complications such as small pulmonary abscesses or persistent asymptomatic bronchitis may have been present to account for the persistence of pneumococci in some of the other cases.

Presumably, the new types which appeared for the first time after sulfonamide treatment was started, particularly those found early in the course of therapy, were also present before that time. Failure to find them may have been due to their presence in relatively small numbers, or to failures of the methods used. As to the strains which made their appearance later, it is not possible to state whether they were originally present or were newly acquired. The fact that some of the strains of pneumococci were found only intermittently even after treatment was stopped would tend to indicate that most of the new strains were probably present earlier.

The persistence of pneumococci was apparently not related to the failure of the patient to develop homologous antibodies. In the first place, almost all of the patients developed antibodies against those of their homologous strains which could be presumed to be the causative agents of their disease, irrespective of whether those strains persisted or disappeared rapidly. Secondly, in the case of some of the strains which made their appearance after treatment was begun antibodies for them were often detected in serums which were obtained before the time when the corresponding strains were first isolated. It is probably justifiable to assume that these antibodies were the results of previous infections with those strains, the infections being either inapparent or manifest but mild. Almost all of the newly acquired strains were of the "higher" types against which antibodies can only rarely be demonstrated in human cases by the agglutination method.<sup>1b</sup>

In the present cases, full therapeutic doses of the sulfonamide drugs were used. While there is no way of judging whether the blood levels obtained were optimal, they seemed to be therapeutically effective. It is not possible, however, to draw definite conclusions from the results of the *in vitro* tests for the susceptibility of the strains. In these tests large numbers of pneumococci were used in a medium which is known to contain inhibiting substances. Other sulfonamide inhibitors are known to occur in the patients' tissues and some of them are present in significant quantities in purulent foci.

It was expected that some of the strains which persisted in spite of

prolonged treatment would become resistant to the action of the sulfonamides. The development of such resistance has been demonstrated in occasional cases of pneumonia,<sup>2c,7</sup> but it seems to be far less frequent than one would suppose. It is of interest that none of the strains tested in the present cases became resistant during treatment, although some of them were readily obtained from sputum and throat cultures after prolonged sulfonamide therapy. It is the practice of some physicians to reduce the dose of sulfonamide and to continue treatment with the smaller doses for several days after the fever subsides. It is possible that under such circumstances or under the régime of continuous small dosage, which is recommended for the prophylaxis of respiratory infections and of rheumatic fever, resistant strains might develop more readily.

The effect of penicillin therapy on the persistence of pneumococci is being studied in this laboratory. With this therapy, too, pneumococci have been found to persist in many cases after doses which are sufficient to bring about rapid clinical improvement.<sup>5</sup>

**Summary and Conclusions.** The persistence of pneumococci in sulfonamide treated cases of pneumonia was studied by the examination of sputum and throat cultures obtained in 43 patients before and at intervals during and after treatment with sulfathiazole or sulfadiazine. Three of the patients were studied during 2 attacks of pneumonia. Considerable variations were found in the persistence of pneumococci in these cases. Of the strains of pneumococci found before the sulfonamide therapy was started, about 30% persisted throughout the period of observation or were obtained intermittently during this time. Three-fourths of the remaining strains could no longer be found after the 3rd day of treatment.

New types of pneumococci which were not found in the pretreatment cultures appeared in the specimens studied during or after sulfonamide therapy in a considerable proportion of the cases. Most of the strains which first appeared during sulfonamide therapy could no longer be found after that treatment was completed.

Multiple types of pneumococci were found more frequently in patients with a history of chronic respiratory infections. In these cases and in those with purulent complications of the pneumonia there was a greater tendency for the pneumococci to persist than in uncomplicated cases.

The persistence of pneumococci was not related to the failure of the patient to develop antibodies for the homologous types.

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## A CLINICAL STUDY OF SENSITIVITY TO SULFATHIAZOLE

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THE therapeutic administration of the sulfonamide drugs may lead to untoward reactions of various types, which, while the individual manifestations vary widely may be divided into three groups on the basis of their pathogenesis: (1) direct toxic effects such as the vomiting induced by sulfapyridine and sulfathiazole, and the cyanosis induced by sulfanilamide; (2) mechanical effects due to precipitation of the drug or its acetyl derivative in the urinary passages; (3) allergic reactions or reactions of hypersensitivity such as drug fever and eruption.

While most of the individual reactions can be assigned to one or another of these groups, some, such as hepatitis and anemia, cannot be easily classified. The present study was undertaken in order to obtain information as to the time of appearance of certain of the allergic reactions to the drugs, as well as of the incidence and time of onset of allergic reactions when the drug was readministered after being withheld for an interval.

Estimates of the incidence of allergic response to sulfathiazole on initial administration vary from 2 to 10%. Lyons and Balberor<sup>3</sup> were the first to point out that many patients who had received an initial course of sulfonamide with impunity, responded to a second administration by the prompt development of drug fever. This occurred in 36% of their 53 cases. Talbot and Adcock<sup>4</sup> reported that of 37 patients given sulfadiazine in 2 courses, 16.2% had drug fever on the second course, while only 8.1% had shown this symptom on the first exhibition of drug. Dowling and Lepper<sup>1</sup> reported an incidence of 16.7% of drug fever with a second course of sulfathiazole in 53 cases but did not state the incidence on the first administration in this same group.

**Procedure.** To obtain data on incidence of allergic reaction on primary administration of the drug, the charts of 472 patients, who had been given sulfathiazole while in the hospital, were examined. Fever without other assignable cause which disappeared on withdrawal of the drug, cutaneous eruptions including erythema nodosum, and conjunctivitis, which were related in a similar way to ingestion of drug, were taken as allergic reactions. One case of nephrosis, in which the possibility of mechanical obstruction to urine flow could be definitely excluded, is included. Cases of gross or microscopic hematuria, anemia, and leukocytosis were not included as allergic phenomena because of uncertainty as to the type of reaction they represent. In order to obtain data on response to readministration of drug, 528 additional charts were examined, a total of 1000.

*Primary Administration.* Table 1 presents all of the untoward effects of the drug in 472 cases. Of this group, 110 patients exhibited some form of reaction; 46, approximately one-half of these 110 patients, had definite sensitivity reactions; of the 71 patients who had reactions other than nausea and vomiting, 65% had allergic responses. Drug fever occurred in practically all cases showing any type of sensitivity reaction. Therefore, we are using it as an index of allergic response in order to simplify the presentation of data.

TABLE 1.—UNTOWARD REACTIONS ON FIRST ADMINISTRATION OF SULFATHIAZOLE

	No. cases	%
Drug fever . . . . .	38	8.05
Skin rash . . . . .	14	2.97
Erythema nodosum . . . . .	1	0.21
Conjunctivitis . . . . .	6	1.28
Nephrosis . . . . .	1	0.21
"Plugging" of urinary tract . . . . .	2	0.42
Renal colic . . . . .	2	0.42
Oliguria . . . . .	15	3.18
Nausea and vomiting . . . . .	71	15.00
Delirium . . . . .	2	0.42
Microscopic hematuria . . . . .	14	2.97
Gross hematuria . . . . .	4	0.85
Anemia . . . . .	1	0.21
Leukocytosis . . . . .	3	0.64
Leukopenia . . . . .	1	0.21
Arthralgia . . . . .	3	0.64
Soreness balls of feet . . . . .	1	0.21

In Figure 1, these febrile responses are shown, distributed by day of onset. Since the number of patients receiving the drug diminished rather rapidly when the time of administration exceeded 3 days, percentages rather than absolute numbers are plotted. The absolute numbers are, however, given in Figure 1. It is evident that the peak incidence of drug fever was reached on the 9th day, the curve dropping sharply after that. Too few patients received drug for more than 11 days to justify calculation of percentages. It is noteworthy also that of the whole number of 38 reactions, over half had their onset between the 7th and 10th days, one-third beginning on the 8th or 9th day. The 1 patient who developed drug fever on the 1st day of administration had had sulfanilamide 1 year before, and perhaps should be classified as a cross-sensitivity case. None of the others, as far as could be determined, had had sulfonamide previously.

*Readministration.* Sulfathiazole was given twice to 103 patients, with an interval of from 2 to 180 days between courses. Detailed data concerning the 22 which had allergic reactions are given in Table 2, and the incidence of reactions on the different courses is summarized in Table 3.

All of the patients who had drug fever on the first administration developed fever on the 1st or 2nd day of readministration of the drug. However, although the great majority of cases once having reacted to the drug develop manifestations of sensitivity when another course of the drug is given, this rule is not absolute. Case 21 had conjunctivitis on the first administration but showed no reaction during a 3-day



second course. Also Case 20 developed drug fever on the second administration but had no reaction on a third course of 4 days.

In 12 patients who reacted to the second administration of sulfathiazole, but had no reaction on the first course, not 1 developed a reaction before a period of 9 days had elapsed from the time the first course was started. This had previously been noted by Lyons and Balberor.<sup>3</sup>

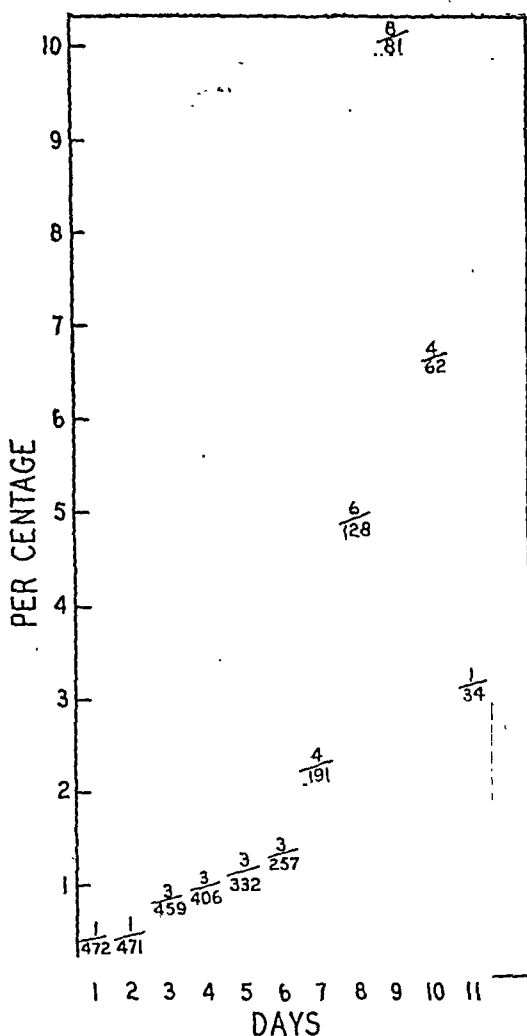


FIG. 1.—Incidence of drug fever distributed by day of onset in 472 cases receiving sulfathiazole for the first time.

We wished to determine what effect the total number of days during which sulfathiazole is administered on both courses might have in relation to development of reactions on the second course. In 12 patients who had drug fever on the second administration and not on the first, the onset of reactions on the second course occurred after from 4 to 15 days of total therapy, with no definite grouping on any individual day. These data suggest that the total time of administration

bears no relation to the time of onset of sensitivity reactions on the second course.

TABLE 2.—READMINISTRATION CASES WITH SENSITIVITY REACTIONS

No.	1st administration				2nd administration					3rd administration				
	Gm.	Days	React.	Day of react.	Inter-val	Gm.	Days	React.	Day of react.	Inter-val	Gm.	Days	React.	Day of react.
1	31	8	..	..	5	9	5	F	2					
2	17	3	..	..	7	9	5	C	5					
								F	1					
								R	3					
3	49	8	..	..	8	4	2	EN	3					
								F	1					
								R	1					
4	36	7	..	..	7	9	7	F	1					
								R	6					
5	50	9	F	9	34	2	1	F	1					
			R	11										
6	44	12	F	7	5	10	1	F	1	210	16	3	F	2
7	42	5	F	4	9	3	1	F	1					
8	2	1	F	1	2	3	1	F	1	1	2	1	F	1
9	48	6	F	?	4	12	1	F	2					
10	9	3	..	..	7	8	4	F	2					
11	13	3	..	..	6	6	2	F	2					
12	10	2	..	..	3	28	5	F	?	330	45	8	R	7
													C	6
													N	
13	52	14	F	?	60	13	3	F	2					
14	7	3	..	..	41	9	6	F	6					
15	64	8	..	..	6	20	3	F	1					
16	7	2	F	5	9	2	1	F	1					
17	19	4	..	..	5	29	9	F	7					
18	79	9	..	..	180	31	6	F	1					
19	31	6	F	?	5	1	1	F	1					
			R											
			C											
20	23	5	..	..	13	45	10	F	10	33	12	4		
21	18	5	C	3	12	10	3							
22	7	4	..	..	3	4	2	F	2					

F = Drug fever. R = Skin rash. C = Conjunctivitis. N = Nephrosis. EN = Erythema nodosum.

TABLE 3.—INCIDENCE OF SENSITIVITY REACTIONS ON READMINISTRATION OF SULFATHIAZOLE

	No. cases	%
Total with no reaction on any course . . . . .	81	78.6
Reaction first time not second . . . . .	1	1.0
Reaction second time not first . . . . .	13	12.6
Reaction on each administration . . . . .	8	7.8
Reaction on first administration . . . . .	9	8.8
Reaction on second administration . . . . .	21	20.4
Total receiving 2 or more courses sulfathiazole . . . . .	103	100.0

The duration of the first course should be examined in relation to the development of reactions on the second course. The data suggest that the incidence of sensitivity reactions on the second administration is no greater with a prolonged first administration than with a short initial course, but there are too few cases to justify a definite conclusion. However, 4 patients who had received sulfathiazole for 4 days or less on the initial administration without reaction, developed signs of

sensitivity within the first 2 days of the second course. Thus, it is important to note that a short initial course, not accompanied by reaction, may effectively sensitize to subsequent administrations.

All of the patients who had drug fever on an initial course developed fever within the first 2 days the second time the drug was given. Also, 9 out of 12 (75%) cases reacting to the second administration and not the first developed drug fever on the 1st or 2nd day of the second course. Fifteen of 19 (79%) of the cases described by Lyons and Balberor developed drug fever within the first 2 days of the second administration. Thus, the brief time in which drug fever appears in many cases after the beginning of the second course points strongly toward the type of reaction seen in individuals already sensitive to an allergen, since it is not readily conceivable that these patients developed sensitivity *de novo* within 2 days. Cases 14, 17 and 20 developed fever on the 6th, 7th and 10th days after the beginning of the second course. It is possible that these cases were not sensitized by their initial course, and that their reactions developed at the time when they would be expected on a primary administration. If it is assumed that the early reactions on the second course are manifestations of preëxisting sensitivity, it can be stated that 9 of 103 patients (8.8%) given 2 courses of sulfathiazole were sensitized by the initial course without displaying any evidence of sensitivity on the first administration. However, the length of the initial course plus the duration of the interval must equal or exceed 9 days in order that a reaction may occur on the second administration.

From our data we are unable to demonstrate any influence of dosage, either total or daily, on the incidence of reactions. However, we have noted that some individuals when sensitive to sulfathiazole will develop drug fever 30 minutes after 0.5 gm. of the drug, whereas others require 4 to 8 gm. in order to produce signs of sensitivity. Thus, it is probably true that individuals vary in their threshold of sensitivity to sulfathiazole.

**Comment.** The peak incidence of drug fever on initial administration of sulfathiazole occurs on the 9th day (9.9%), after which the incidence of this reaction declines sharply. Therefore, if a patient has received the drug for 9 days without developing drug fever, the chances that he will have fever subsequent to this on the same administration diminish rapidly.

It has been suggested that the incidence of drug fever on the second administration of sulfathiazole is enhanced by an interval between courses. If the readministration cases that developed fever on the first course are withheld from consideration, then the figures are biased by the removal of the cases which we know would develop sensitivity reactions on the second administration. Therefore, a lower incidence of reactions on subsequent administrations would be expected in this group. However, the incidence of fever in this biased group is higher (12.6%) than that in the cases receiving sulfathiazole for the first time (8.1%). Furthermore, 75% of our sensitivity reactions occurred

within the first 2 days of readministration. It is highly improbable that three-quarters of the reactions would appear within a 2-day period unless there were a preëxisting allergic state. Therefore, we believe that an interval between courses plays a distinct rôle in the demonstration of sensitivity.

The data which have been presented lend strong support to the thesis advanced by Longcope<sup>2</sup> that these allergic reactions to sulfonamides belong in the same class of diseases as serum sickness. An important and practical consideration seems to be that many more individuals are sensitized to the drugs than would be predicted from examination of data on initial administration.

**Summary and Conclusions.** Of 472 patients who received one course of sulfathiazole, 110 exhibited some form of reaction to the drug and approximately one-half of these had allergic reactions.

The percentage of patients developing drug fever on any one day of therapy is given. The curve rises to a peak of 9.9% on the 9th day and thereafter drops sharply. Thus, if a patient has had no reaction after 9 days of therapy, his chances of developing one subsequently on the same administration diminish rapidly.

Of 103 patients receiving sulfathiazole twice, with an interval of from 2 to 180 days between courses, 22 patients exhibited sensitivity reactions.

In the patients showing manifestations of sensitivity on the second course, drug fever occurred within the first 2 days of readministration in all of the patients who had fever on the first course. Three-quarters of them had, however, had no reaction on the first course.

Of the patients who reacted to the second administration but not the first, none developed a reaction before 9 days had elapsed from the time the first course was started.

Evidence has been presented which suggests that the appearance of sensitivity reactions on the second course is not related to the total time the drug is administered, or to the absolute duration of the interval between courses.

Sensitivity reactions on readministration may follow an initial course which may be as short as 2 or 3 days.

No influence of dosage on the incidence of sensitivity reactions was demonstrated.

The short time between the beginning of readministration and appearance of drug fever is regarded as evidence that an allergic state was present at the time the second course was started. An interval between courses serves to demonstrate that an initial administration has sensitized an individual to subsequent courses of the drug.

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## FAILURE OF PENICILLIN IN RHEUMATOID ARTHRITIS

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ALTHOUGH the etiology of rheumatoid arthritis is unknown, many factors suggest that this may be at least in part an infectious process. Such a relationship is suggested by the rapid sedimentation rate, signs of inflammation in the affected joints, fever, tachycardia, loss of weight, positive agglutination reactions to Lancefield group A hemolytic streptococci in more than half of the cases when the disease has been present for 6 months or longer, and a history of preceding upper respiratory infection in some instances.

At present, therapy for rheumatoid arthritis is far from satisfactory. Although most rheumatologists are agreed upon the use of such measures as physical and mental rest, rest of the affected joints, adequate physical therapy, orthopedic care, a sensible high caloric, high vitamin, anticonstipation diet, psychotherapy and symptomatic care, various pseudoremedies have been tried in the past several decades with, in most instances, very little measure of actual benefit. Such substances as bee venom, sulfur, chaulmoogra oil and similar preparations are no longer employed in most arthritic clinics. Sulfonamides have not proved of value in rheumatoid arthritis. The supposed specific immunizing value of vaccines has also been disproved when it was shown that similar symptomatic improvement followed comparable doses of physiologic saline given subcutaneously or intravenously. The value of massive doses of vitamin D in rheumatoid arthritis is questionable; the majority of the larger arthritis clinics believe that no permanent beneficial effect is produced.

The single chemotherapeutic agent which appears to be of definite value at present in rheumatoid arthritis is parenterally injected gold in the form of gold salts. However, gold salts are not the final answer to the therapy of rheumatoid arthritis inasmuch as they are toxic; some patients with rheumatoid arthritis are not improved following gold therapy, and relapses are not infrequent following cessation of chrysotherapy.

**Methods.** Six patients with typical rheumatoid arthritis were selected; 5 of these were females. In 5 of these individuals, the rheumatoid arthritis was of at least 4 years duration and 3 of the patients had been followed carefully throughout this period. In 1 instance, the rheumatoid arthritis had begun in childhood (Still's disease) and had later become quiescent—only to flare up 5 years later. In another patient, the typical rheumatoid arthritis was apparent for only 8 weeks prior to treatment.

In all instances, penicillin was injected intramuscularly (into the gluteal or deltoid muscles) every 3 hours, day and night for at least 2 weeks. Total dosage was never less than 100,000 units per 24 hours. In 2 of the patients, 200,000 units was given per 24 hours for 1 week, in addition to a further 2 weeks or more of therapy with 100,000 units per 24 hours. Three patients were treated continuously for 4 weeks each; 2 were treated with penicillin for 3 weeks, and 1 received penicillin for only 2 weeks.

The penicillin was dissolved in physiologic saline so that each 100,000 units were mixed with 16 cc. of physiologic saline: when a dose of 100,000 units per day was employed, 2 cc of this mixture was given every 3 hours day and night. The solution was freshly prepared each day, and was kept in the ice-box between injections.

Sedimentation rates were performed every 4 to 7 days by the Rourke-Ernstene method.

All of the patients were hospitalized; 3 were ward patients and 3 were in private or semi-private rooms. All of the patients showed active rheumatoid arthritis clinically when penicillin therapy was begun and sedimentation rates were repeatedly elevated in all instances before the onset of therapy. The typical findings of rheumatoid arthritis were evident: spindle shaped swellings of multiple, symmetrical proximal interphalangeal joints, involvement of the metacarpophalangeal joints, low grade fever, tachycardia, loss of weight, muscular atrophy in some instances, demineralization of bones, soft tissue swelling and narrowing of the joint space by Roentgen examination, anemia and rapid sedimentation rates.

One patient who had been treated for long periods by massive doses of vitamin D (in another institution) showed multiple areas of calcification in both kidneys. One patient had received gold therapy in another hospital several years prior to this period but was forced to discontinue chrysotherapy because of the development of purpuric manifestations. The other 4 patients had been treated by conservative measures.

During the penicillin therapy, conservative measures such as physical therapy, a sensible diet, splinting of affected joints and the use of mild analgesics when required were continued.

**Case Reports.** CASE 1. O. F., aged 22, colored female, was admitted on 8/25/44. She was first seen in 1937 at the age of 15 at which time her chief complaints were stiffness and swelling of the wrists and knees, and fusiform swelling of the proximal interphalangeal joints of most of the fingers. She had lost 40 pounds in the 2 years prior to that time. Physical examination in 1937 showed marked emaciation, fusiform swelling of the proximal interphalangeal joints, swollen, stiff ankles and elbows, and marked muscular wasting. The patient was treated conservatively and her general condition improved gradually.

In the spring of 1944, there was a recurrence of activity of her arthritis with marked increase in joint pain, swelling and stiffness, fever, rapid sedimentation rate, tachycardia, effusion in both knee joints, considerable limitation of motion in the elbows, hips and knees and advanced deformities of the hands. Roentgen examination revealed typical findings of long-standing rheumatoid arthritis with demineralization of bone and marked narrowing of the joint spaces.

Corrected sedimentation rates (using the simplified Rourke-Ernstene method) prior to the administration of penicillin were: 7/3/44, 64 mm.; 7/6, 49 mm.; 7/10, 55 mm.; 8/24, 60 mm.; 8/31, 50 mm.; 9/1, 48 mm.

Penicillin therapy was begun on 9/2/44; 100,000 units was given daily intramuscularly in divided doses every 3 hours day and night for a period of 28 days. Corrected sedimentation rates following penicillin therapy were: 9/8, 44 mm.; 9/13, 42 mm.; 9/18, 60 mm.; 9/22, 47 mm.; 9/25, 44 mm.; 9/28, 44 mm. (penicillin therapy was stopped on 9/30); 10/10, 57 mm.

The rheumatoid arthritis was not evidently affected either subjectively or objectively during or within 4 weeks following the termination of a total of 2,800,000 units of penicillin. Sedimentation rates remained essentially the same.

CASE 2. M. E., white married female, aged 32, was admitted 6/20/44, with findings typical of rheumatoid arthritis. She had been well until the spring of 1938, at which time she developed swelling and stiffness of multiple, symmetrical, proximal interphalangeal and metacarpophalangeal joints, followed by pain, swelling and stiffness in the knees, feet and other joints. Treatment at another institution included (over a period of several years) injections of

sulfur, vaccine and gold. The latter was stopped because of the development of purpuric spots. The patient was fairly well from June 1942 until May 1944 at which time there was a marked aggravation of her joint pain, swelling and stiffness in multiple joints (hands, elbows, wrists, knees and ankles). The patient was forced to go to bed in June 1944. She had lost 10 pounds in the month prior to the present admission.

Physical examination on this admission revealed tender, swollen knees, wrists, elbows, ankles, feet and proximal interphalangeal joints and metacarpophalangeal joints, with ulnar deviation of the fingers, and marked limitation of motion in the elbows and knees.

Laboratory examination showed a moderate hypochromic anemia, normal renal function, typical Roentgen appearance of rheumatoid arthritis and increased sedimentation rate. Sedimentation rates prior to penicillin therapy were: 6/21, 96 mm.; 7/3, 84 mm.; 7/10, 98 mm.; 7/19, 85 mm.; 7/26, 90 mm.; 7/28, 70 mm.

Penicillin was begun on 7/29/44 in divided doses intramuscularly every 3 hours day and night; 100,000 units was given each 24 hours from 7/29/44 until 8/17/44 at which time the dose was increased to 200,000 units per day; this latter dose was continued for an additional week. The patient received a total of 3,300,000 units of penicillin over a period of 4 weeks. Sedimentation rates following penicillin were as follows: 8/3, 75 mm.; 8/8, 68 mm.; 8/11, 75 mm.; 8/23, 85 mm.; 8/28, 100 mm.

There was no apparent improvement either subjectively or objectively in the arthritic picture during penicillin therapy or within a period 7 weeks following the conclusion of penicillin therapy. The patient thought that she felt somewhat stronger following the penicillin therapy but could notice no change in the pain, swelling or stiffness.

CASE 3. S. E., a white male of 34, was admitted to the University Hospital 4/24/44 with a typical picture of rheumatoid arthritis. The patient was well until 1940 at which time he noticed intermittent swelling of the ankles and knees. This joint swelling, pain and stiffness gradually appeared in the hands, wrists, elbows and other joints. Within the year prior to admission, there was considerable limitation of motion and the symptoms progressed to such a stage that crutches were required for walking. He lost 30 pounds of weight in the past year.

Physical examination revealed typical fusiform swelling of the proximal interphalangeal joints of the fingers, metacarpophalangeal joint swelling, ulnar deviation of the fingers, marked swelling and limitation of motion of the elbows, knees and ankles and evidence of marked loss of weight and muscular atrophy.

Laboratory tests revealed a moderate hypochromic anemia, typical Roentgen findings of rheumatoid arthritis and a rapid sedimentation rate.

Sedimentation rates prior to penicillin therapy were: 5/8/44, 39 mm.; 6/5, 58 mm.; 7/17, 65 mm.; 7/26, 50 mm.; 7/28, 59 mm.

Penicillin was begun on 7/29/44 and a total of 100,000 units was given intramuscularly each day from 7/29/44 until 8/12 (a total of 1,400,000 units of penicillin). Sedimentation rates following the injection of penicillin were: 7/31/44, 53 mm.; 8/3, 54 mm.; 8/10, 55 mm.; 8/18, 60 mm.

No subjective or objective improvement was seen during the course of penicillin therapy, or for a period of 2 months following this therapy.

CASE 4. B. M., a married white female of 35 years, developed pain, swelling and stiffness in the right wrist 7 years ago. Since that time, there has been progressive involvement of the feet, knees, elbows, hands and other joints. In the past year, she lost 12 pounds in weight. Physical examination revealed fusiform swelling and tenderness of the wrists, elbows, knees and ankles. There was a moderate hypochromic anemia. Roentgen ray examinations revealed changes typical of rheumatoid arthritis in multiple joints with demineralization of bones, narrowing of joint spaces and fusiform soft tissue swelling.

Sedimentation rates prior to penicillin therapy were: 7/18/44, 38 mm.; 7/21, 35 mm.; 7/26, 40 mm.; 7/30, 33 mm.

Penicillin was begun on 7/31/44 and was continued in a total daily dosage of 100,000 units until 8/29/44—a total of 2,900,000 units being given. Sedimentation rates following penicillin therapy were: 8/2, 36 mm.; 8/4, 42 mm.; 8/8, 40 mm.; 8/14, 37 mm.; 8/17, 35 mm.; 8/21, 45 mm.; 8/28, 38 mm.; 9/5, 42 mm.

There was no apparent improvement either subjectively or objectively during the course of penicillin therapy.

In contrast to the failure with penicillin, it might be worth while recording the results of gold administration in this patient. Gold therapy (calcium aurothiomalate) was begun on 9/8/44 (10 days after the last injection of penicillin). After the 4th week of chrysotherapy, the patient began to notice much less pain and swelling in the affected joints (particularly the hands, knees and ankles) and the swelling in these joints was visibly decreased. The sedimentation rate began to fall at this time and had returned to normal after 6 weeks of gold therapy. Not over 25 mg. of calcium aurothiomalate was used at any one dose. Injections of gold salts were given intramuscularly each week after the first 2 weeks (during which early period 2 small injections—10 mg. each—were given each week). The details and results of chrysotherapy in rheumatoid arthritis will form the basis of a separate report.

The sedimentation rates following institution of gold therapy were: 9/12/44, 48 mm.; 9/19, 43 mm.; 9/25, 40 mm.; 10/2, 28 mm.; 10/9, 22 mm.; 10/16, 12 mm.; 10/23, 10 mm.; 3/10/45, 8 mm.

This patient has improved steadily both subjectively and objectively since the 4th week of gold therapy.

CASE 5. This 47 year old white married woman (S. H.) was admitted 7/27/44 with a typical rheumatoid arthritis of 12 years duration. She had previously received various forms of treatment, including several courses of "Ertron" capsules (containing 50,000 units of vitamin D) varying from 3 to 6 per day for some months at another institution. Despite therapy, she had progressed intermittently so that on admission, there was a moderate amount of crippling deformity of the fingers with ulnar deviation of the hands; swelling, tenderness and flexion contracture of the knees; marked limitation of motion and tenderness of the elbows, shoulders, feet and other joints. Urogram revealed multiple, small urinary calculi bilaterally similar to the calcium deposits seen in hyperparathyroidism. It is distinctly possible that these may have resulted from the massive doses of vitamin D which she had taken.

Roentgen examination revealed marked demineralization of bones, marked narrowing of the joint spaces, cystic areas near the ends of the bones, soft tissue fusiform swelling of the proximal interphalangeal joints and the evident deformities. A moderate hypochromic anemia was present. Sedimentation rates prior to penicillin therapy were: 7/27, 96 mm.; 7/29, 104 mm.; 8/1, 94 mm.

Penicillin was then begun intramuscularly on 8/2/44 and was continued in a total daily dosage of 100,000 units until 8/16/44, at which time the dose was increased to 200,000 units per day for an additional 8 days—a total dosage of 3,000,000 units of penicillin. Sedimentation rates following penicillin therapy were: 8/8/44, 110 mm.; 8/16, 130 mm.; 8/21, 100 mm.; 8/24, 114 mm.

The patient left the hospital at this time. A sedimentation rate 5 weeks later, 10/6/44, was 115 mm. There was no evident subjective or objective improvement in the arthritic picture.

CASE 6.—M. A., a 35 year old married woman, developed slight pain and swelling of the proximal interphalangeal joints of the second, third and fourth fingers of the left hand about the end of June 1944. There were also mild aches and pains in the ankles and knees. The patient had lost 10 pounds of weight in the following month and showed on laboratory examination a moderate hypochromic anemia and a slightly increased sedimentation rate. Roentgenograms of the hands showed only slight bony demineralization and fusiform soft tissue swelling of the proximal interphalangeal joints. There was no evidence of gonorrhea; gonococcus complement fixation test was negative. There was no history of rheumatic fever. Sedimentation rates were as follows: 8/15, 28 mm.; 8/22, 25 mm.; 8/29, 35 mm.

Although some early cases of rheumatoid arthritis may respond to con-



servative care with rest of the patient and of the involved joints, physical therapy, adequate caloric and vitamin intake and symptomatic care, such improvement is not usually rapid. It was, therefore, thought that this patient represented a suitable early case of rheumatoid arthritis for trial of penicillin therapy. Penicillin was begun on 8/30/44 and was continued in a daily total dose of 100,000 units per day for 3 weeks (a total dose of 2,100,000 units). During this period, the joint pain and swelling gradually increased and new joints became involved. The stiffness, pain and swelling of the fingers increased definitely during such therapy. Sedimentation rates during and after penicillin therapy were: 9/5/44, 32 mm.; 9/12, 38 mm.; 9/19, 44 mm.; 9/26, 46 mm.; 10/10, 40 mm.; 10/19, 43 mm.

The arthritis definitely progressed and became worse during penicillin therapy.

**Comment.** Six patients with typical rheumatoid arthritis were treated for from 2 to 4 weeks with penicillin during the acute or sub-acute stage of their disease. The total dose of penicillin varied from 1,400,000 to 3,300,000 units. Five of the 6 patients received more than 2,000,000 units. In all cases, the penicillin was administered intramuscularly in divided doses every 3 hours day and night.

All of the patients showed joint swelling and pain and an increased sedimentation rate before penicillin therapy. There was no evidence that penicillin altered the course of the disease in any of the patients. In 5 of these patients the arthritis had been present for periods of 4 years or more; all of these showed activity of their rheumatoid arthritis at the time of penicillin administration. The sixth patient presented an early rheumatoid arthritis of only 8 weeks duration prior to penicillin therapy. In Case 1, the arthritis had been inactive for several years but the active process recurred 5 months prior to penicillin administration.

**Summary.** There was no subjective or objective evidence of improvement in 6 patients with active rheumatoid arthritis following the administration of penicillin intramuscularly in total doses varying from 1,400,000 to 3,300,000 units given over periods varying from 2 to 4 weeks.

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## FOCAL ELECTROENCEPHALOGRAPHIC CHANGES DURING THE SCOTOMAS OF MIGRAINE

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In a recent communication<sup>1</sup> we have described a migraine-like syndrome complicating decompression sickness. This was characterized by scintillating scotomas, homonymous visual field defects, rarely other focal neurologic signs, and headache, the latter usually contralateral to the scotomas. These symptoms always occurred after

decompression sickness had developed but they were unrelated to altitude. Most often they developed 5 to 30 minutes after descent, but when they did develop at altitude their course was the same whether the subject remained at altitude or was brought down. The

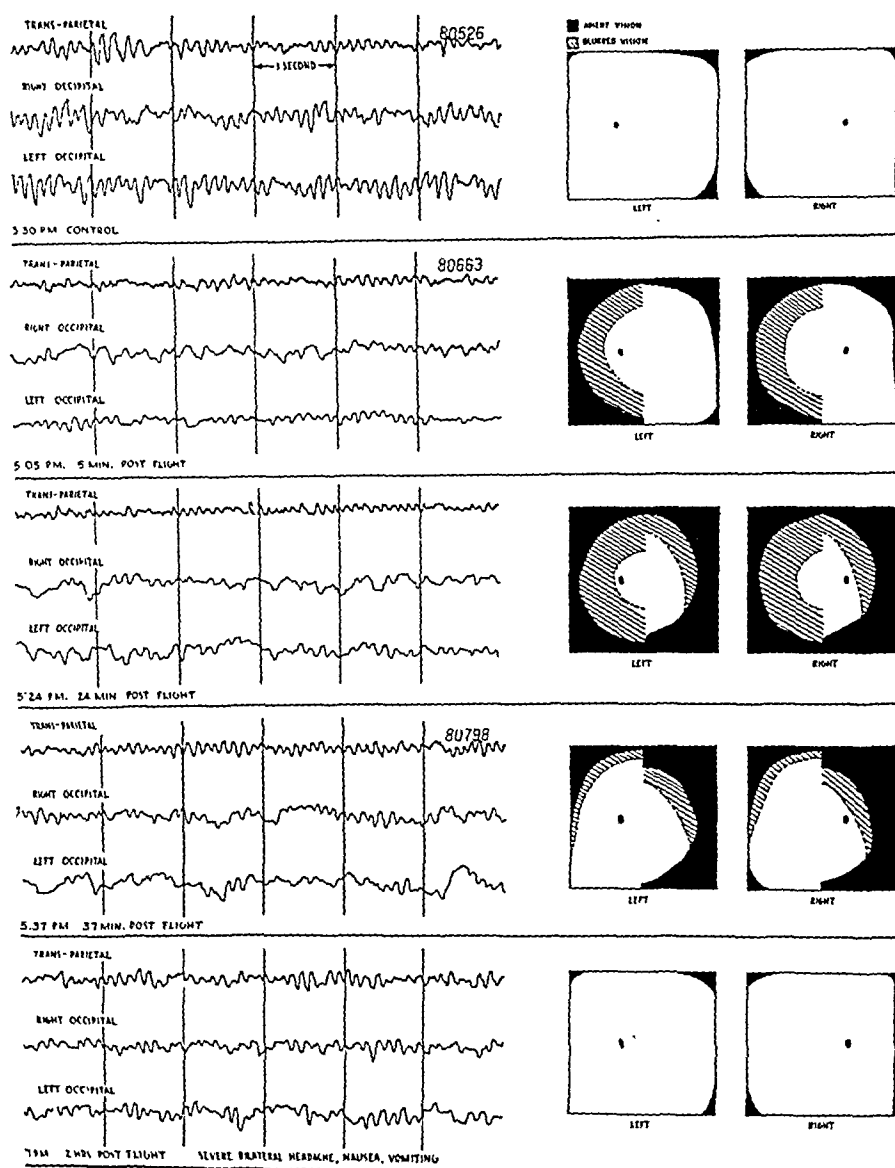


FIG. 1.—Electroencephalogram and visual fields during the scotoma-migraine syndrome complicating decompression sickness. Note the appearance of irregular 4 to 7 per second waves from the occipital region contralateral to the visual field defect. The transparietal tracing remained unchanged. The electroencephalogram was normal during the period of severe headache, nausea, vomiting.

reaction tended to occur repeatedly in certain individuals and not at all in others. A statistical analysis of the past incidence of headaches having the character of migraine regardless of frequency or intensity revealed a highly significant positive correlation among the scotoma

susceptible subjects. It is our opinion that this reaction is mediated through a vascular mechanism which is similar to, if not identical with, that described in clinical migraine by Wolff and his associates.<sup>3</sup>

Electroencephalographic studies in 2 instances of this syndrome revealed focal changes in the cortical areas corresponding to the neurologic signs and symptoms. The homonymous visual field defects were accompanied by slowing and irregularity of the potentials arising from the contralateral occipital cortex. The electroencephalographic abnormalities continued as long as the neurologic signs persisted, following which the record returned to normal and remained normal during the headache. (See Fig. 1.) Gibbs,<sup>2</sup> in a discussion of these studies, remarked that he had been unable to obtain any comparable electroencephalographic findings during the visual disturbances of clinical migraine. Because of the close similarity in all other respects between this syndrome complicating decompression sickness and clinical migraine, it seemed important to obtain similar observations in the latter condition.

**Method.** Electroencephalograms were obtained on 3 subjects with migraine while experiencing scotomas. In all instances abnormalities were demonstrated in the corresponding occipital cortex. Electrodes were applied at the lateral tips of theinion which were considered to be reasonable approximations of the projection of each visual cortex on the skull. In 1 case 2 parietal electrodes were also applied. Because of the short duration of the scotomas the electrodes were applied as quickly as possible and records taken until a normal pattern had been regained. A 3-channel electroencephalograph, constructed by Mr. Albert Grass, was used.

**Case Reports.** **CASE 1.** A 38 year old physician with history of typical migraine dating back to age 14. Mother and maternal aunt both suffered from severe migraine. Typical attacks are heralded by drowsiness on arising in the morning. This is then followed by slowly increasing hemicrania, accompanied by nausea, salivation, chilliness, breathlessness, and evacuation of bladder and bowel. The pain is bright and bounds with the pulse. The hemicrania can be relieved by occlusion of the ascending temporal branches of the external carotid artery on the same side. The entire attack usually occupies  $\frac{1}{2}$  day. For years the attacks have occurred about once a month.

Scintillating scotomas as prodromata of the headache were first observed about 13 years ago, and in all 30 to 40 such attacks have occurred during the subsequent 5 years. The scotoma was usually on the right and lasted 10 to 20 minutes. Other prodromata have been numbness and tingling of the right upper extremity, 11 years ago, and expressive aphasia (9 years ago); each episode lasted about 30 minutes and was followed by a severe headache.

On June 30, 1944, the patient noted onset of scintillation of vision in the right upper visual field. Gross confrontation revealed a homonymous visual field defect in this area. Scintillation was apparent with the eyes either open or closed. Electrodes were applied as quickly as possible at the lateral borders of theinion; monopolar tracings were obtained from the right occipital and the left occipital regions and a bipolar tracing from the transoccipital. These are illustrated in Figure 2. The scintillation, which lasted a total of 15 minutes, was present, but receding peripherally, during the first 3 minutes of recording. The tracing from the left occipital region revealed irregular low voltage slow activity which was not present on the right side. As the scotoma disappeared to the periphery the left occipital tracing revealed slower and higher voltage activity for 1 minute and then progressively improved; 6 minutes after scintillation had vanished the tracings from both occipital regions were normal and synchronous. Left-sided headache began shortly thereafter.

**Comment on Case 1.** Focal electrical abnormalities arising from the occipital cortex corresponding to the homonymous visual field defect are clearly demonstrated in this case. The fact that the electroencephalogram became more abnormal during the first minute after the scotoma had disappeared is probably explained by inaccurate electrode placement. Were the electrodes placed over a relatively silent area of occipital cortex, increase in abnormality as the disturbance receded from the visual field seems entirely plausible. It will be noted that this phenomenon lasted only 1 minute after subjective appreciation of scintillation had disappeared and that complete return of the electroencephalogram to normal required only 5 minutes.

#### CASE I. MIGRAINE

10 AM: RIGHT HOMONYMOUS SCINTILLATING SCOTOMA; ONSET, 9:46 AM

RIGHT OCCIPITAL

Nº 82419

LEFT OCCIPITAL

10:01½ A.M.: 30 SEC AFTER SCOTOMA

RIGHT OCCIPITAL

Nº 82429

LEFT OCCIPITAL

10:08 A.M.: 7 MIN. AFTER SCOTOMA.

RIGHT OCCIPITAL

Nº 82470

LEFT OCCIPITAL

FIG. 2.—Case 1. Note the low voltage slow waves from the left occipital region during right homonymous scintillating scotoma. For the first minute after the scotoma disappeared the voltage of the slow waves became higher. Seven minutes later the record was completely normal. Headache had not yet begun.

**CASE 2.** A 39 year old physician had experienced occasional mild headaches in childhood. Seven years ago he first experienced severe hemicrania associated with nausea and vomiting, lasting 5 to 6 hours. A second severe attack occurred 6 months later. Many very mild unilateral headaches have occurred since then. Two years ago the development of decompression sickness during exposure to high altitude in a decompression chamber was followed on 5 occasions by scintillating scotomas, homonymous visual field defects, and subsequent mild contralateral headache. Since then the patient has had 4 episodes of spontaneous scotoma, 1 on the left, 3 on the right. All occurred in the morning and were followed by mild contralateral headache lasting the remainder of the day.

At 9:30 A.M., June 8, 1944, onset of scintillating scotoma in the upper quadrant of the visual field was noted. Brief confrontation revealed a right homonymous upper quadrantic defect. Electrodes were applied as in Case 1. After some tracing had been obtained, parietal electrodes were also applied. The results are illustrated in Figure 3. Tracings were obtained during the

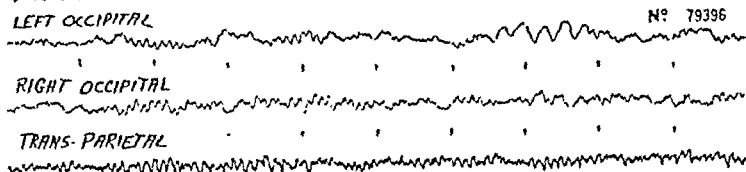
last 5 minutes of the scotoma, as it receded peripherally. Irregular, low voltage slow waves, frequency, 4 to 7 per second, with some admixture of alpha activity, were obtained from the left occipital region. Regular, 9 to 10 per second alpha activity was obtained from the right occipital region. As the scotoma disappeared, a few bursts of slow waves were still to be seen from the left occipital, while the activity from the right occipital and transparietal regions remained normal. With the appearance of left-sided headache the electroencephalogram returned to normal.

#### CASE II: MIGRAINE

9:40 A.M. RIGHT HOMONYMOUS SCINTILLATING SCOTOMA: ONSET 9:30 A.M.  
LEFT OCCIPITAL



9:45 A.M. SCOTOMA DISAPPEARING



9:55 A.M. LEFT-SIDED HEADACHE; NO SCOTOMA

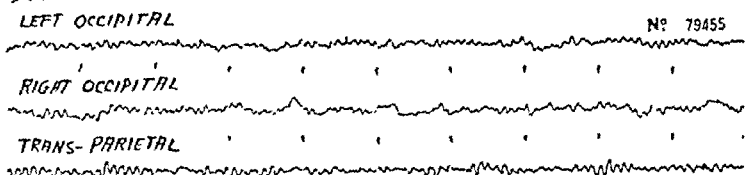


FIG. 3.—Case 2. Absent alpha activity and irregular low voltage slow waves from the left occipital cortex during right homonymous scintillating scotoma. Tracings from the left occipital and transparietal regions were normal. Ten minutes after the scotoma had disappeared the electroencephalogram was normal. Left-sided headache had begun.

CASE 3. A 26 year old resident physician has experienced episodes of scintillating scotoma and headache during the past 7 years. These incidents often have their onset during reading and he is aware of gross visual field defects. The headache is sharp, moderately severe, radiates from frontal to occipital region, and is contralateral to the scotoma. The scotomas are sometimes bilateral. The headache is usually alleviated by 10 to 20 gm. of aspirin or  $\frac{1}{2}$  gr. codeine within 1 hour. Gastro-intestinal symptoms have not been present. These episodes have occurred as often as 15 times a year often during periods of emotional tension.

At 3:15 P.M., June 17, 1944, a scintillating scotoma appeared in the right homonymous visual field. This gradually moved to the periphery, but at the end of 1 hour was still present. At 4:30 P.M. electrodes were applied and electroencephalographic tracings were obtained. At this point the subject indicated the appearance of the scotoma in the extreme periphery of the right homonymous visual field which came and went at 20 to 30 second intervals, lasting 10 to 15 seconds at a time. At less frequent intervals slight scintillation was noted in the left field as well. The subject was asked to indicate the appearance and disappearance of the scotoma. The findings are illustrated in Figure 4. With the appearance of scintillation on the right, the tracing from the left occipital

region revealed loss of alpha activity and low voltage slow waves. Alpha activity returned when the scintillation disappeared. Similar, but less striking alterations were recorded from the right occipital region during the fluctuating left-sided scintillation. Twenty minutes of tracing were obtained. The fluctuating scintillation lasted another 20 minutes and was followed by bilateral headache. An electroencephalogram obtained 2 days later when no symptoms were present revealed sustained and symmetrical alpha activity from both occipital regions.

### CASE III : MIGRAINE

4:30 P.M. RIGHT SCINTILLATING SCOTOMA: ONSET, 3:15 P.M.

LEFT OCCIPITAL

Nº 84417

RIGHT OCCIPITAL

10 SECONDS: RIGHT SCINTILLATING SCOTOMA.

LEFT OCCIPITAL

Nº 84418

RIGHT OCCIPITAL

20 SECONDS: NO SCOTOMA.

LEFT OCCIPITAL

Nº 84419

RIGHT OCCIPITAL

230 SECONDS: RIGHT AND LEFT SCINTILLATING SCOTOMAS.

LEFT OCCIPITAL

Nº 84440

RIGHT OCCIPITAL

240 SECONDS: RIGHT SCINTILLATING SCOTOMA.

LEFT OCCIPITAL

Nº 84441

RIGHT OCCIPITAL

250 SECONDS: NO SCOTOMA.

LEFT OCCIPITAL

Nº 84443

RIGHT OCCIPITAL

2 DAYS LATER: NO SCOTOMA; NO HEADACHE

LEFT OCCIPITAL

Nº 84504

RIGHT OCCIPITAL

Fig. 4. Case 3. After 75 minutes right and left scintillating scotomas were in the extreme periphery of the visual fields and were waxing and waning in intensity. With each reappearance of the scintillation there was loss of alpha activity and low voltage slow activity from the corresponding occipital cortex. This was observed more consistently from the left occipital cortex than from the right. Two days later sustained alpha activity was found arising from both occipital regions and there were no symptoms.

**Discussion.** Although only 3 cases are presented, the results are so clear-cut as to allow little question as to their validity. Indeed, considering the difficulties of timing and of electrode placement the ease with which the focal abnormalities were demonstrated was unexpected.

Schumacker and Wolff<sup>3</sup> have presented convincing evidence that the focal neurologic signs of migraine, of which scintillating scotoma are the most common, are the result of spasm of intracerebral vessels, while the headache results from dilation of the pain-sensitive extracranial branches of the carotid artery. More specifically, the scotoma are thought to result from spasm of branches of the posterior cerebral artery, with ischemia of portions of the occipital cortex. The homonymous nature of the visual field defects, the sparing of central vision, the peripheral spread of the scotoma, and the efficacy of vasodilator drugs in relieving the scotoma all favor such a mechanism. The demonstration of irregular, slow waves in the electroencephalogram from the occipital cortex corresponding to the visual defect offers additional evidence for the existence of such areas of local cortical ischemia. The prompt return of the electroencephalogram to normal following scotoma of brief duration and the remarkable simultaneous waxing and waning of both the scotoma and the electroencephalographic abnormalities following a scotoma of longer duration, as illustrated in Case 3, are quite consistent with the behavior of vasospastic phenomena.

The syndrome complicating decompression sickness resembles clinical migraine so closely that we have postulated an identical mechanism and have ventured the suggestion that it may possibly be true migraine provoked in susceptible individuals by decompression sickness. Indeed, the failure of previous investigators to demonstrate electroencephalographic changes during the scotoma of clinical migraine represented the chief point of difference between the two syndromes. The data of this paper obviate this difficulty. The only significant difference now remaining between the two syndromes relates to the relative intensity of the focal neurologic (vasospastic) signs and of the headache (vasodilation). In the syndrome complicating decompression sickness the vasospastic phenomena are prominent while the headache is often mild; in clinical migraine the reverse is more often true.

**Summary.** Abnormal electrical activity from one occipital cortex has been demonstrated in 3 instances of spontaneous scintillating scotoma with homonymous visual field defect occurring during attacks of clinical migraine. Irregular, slow waves were recorded from the contralateral occipital cortex while regular normal activity was recorded from the ipsilateral occipital cortex, and from both parietal regions. With disappearance of scotoma the electroencephalographic abnormalities also disappeared, although in 1 case the pattern became more abnormal for the first minute after the scotoma had disappeared before returning to normal. It was thought this might relate to inaccurate electrode placement. The record was normal during the beginning of the headache.

These data confirm the results previously obtained during examples

of a migraine-like syndrome occurring as a complication of decompression sickness and further emphasize the analogy between that syndrome and clinical migraine. One of the subjects in this report had also experienced scotomas and headache after decompression sickness. The results also are consistent with the vasospastic nature and cortical origin of the scintillating scotoma of migraine as postulated by H. S. Wolff and his associates.

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## INITIAL CARDIAC EXAMINATION OF 23,000 INDUCTEES AND VOLUNTEERS

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MANY cardiac problems of wartime have been presented to date. In general, White<sup>22a</sup> discussed the Army, and Duncan<sup>6</sup> the Navy viewpoints. From the individual service examiners have come the reports by Ungerleider, Duhigg and Gubner,<sup>20</sup> Master,<sup>13</sup> and Wilburne and Ceccolini.<sup>23a</sup> Statistical studies of selective service records were those of Rowntree.<sup>15</sup>

More important, from the cardiac standpoint, was the report of the reexamination of 4994 men disqualified for general military service because of the diagnosis of cardiovascular defects.<sup>11a</sup> This combined study,<sup>8a</sup> made by special medical advisory boards in Boston,<sup>22b</sup> Chicago,<sup>8b</sup> New York,<sup>11c</sup> Philadelphia,<sup>19</sup> and San Francisco,<sup>10</sup> was subsequently published in detail. The findings of an initial cardiac examiner have not been presented.

From February 5, 1943, to June 21, 1944, I, among many others, had the unusual privilege of serving as a civilian physician on part-time, temporary duty, attached to a chest section of a medical unit at the Armed Forces Induction Station in Chicago. Civilian doctors constituted the backbone of the examining groups at these stations.<sup>15c</sup> During this period I examined 23,000 men between the ages of 17 and 38 years who were sent to the Induction Station by the Selective Service Boards in the State of Illinois. The men included those who

\* The opinions and assertions expressed herein are those of the writer, and are not to be construed as those of any member or branch of the Armed Forces.



were going into the Army, Navy, Marine Corps, and Coast Guard, if accepted for service.<sup>18</sup> This study does not include men of 38 years and over who volunteered for special units, such as the Seabees and Ship Repair. The 23,000 men were fairly representative of the normal male adult population in that age group.

Although the chest section was responsible for all heart and lung conditions, asthma, and hay fever, questions concerning which were asked of all examinees, this report is based only on the cardiac examination. A routine procedure was followed which precluded the omission of any part of the cardiac examination. All men were asked the same questions as to previous known heart trouble, the cardiac area was auscultated at various points, and the blood pressure was estimated. Even before this was done, the cardiac examination really began as the man stepped into view. Unusual apprehension, malar flushing, cyanosis of the lips, and abnormal pulsations in the neck, arms, or chest were noted. Such signs were rare among this large group, but the notation of any of these findings attracted much closer attention to the subject.

The task of the civilian examiner was to weed out those with a history and/or findings of heart disease according to the mobilization regulations. This job was of much greater significance than it seemed to be at first. During the period stated I examined on the average of 20 men per hour; the average number of hours worked per day was 4.7. The constant problem of error, in that one might do an injustice to both the Armed Forces and the examinee by overlooking any cardiac disturbances in such a steady flow of men, had to be kept in mind at all times.

Heart disease is often perfectly compatible with normal activity, even for the strenuous physical demands occasioned by service in the Armed Forces. However, because of the eventual limitations which tend to develop in most types of heart disease, it was not deemed advisable to accept men with definite heart disease for service, since permanent obligations are assumed by the government for its military personnel.<sup>20</sup> All men were subjected to a chest photo-roentgenogram, but only those weeded out for cardiac reasons received further diagnostic work-up along these lines, which was at the discretion of the medical officers in the chest section.

Among the 23,000 men which I examined there were 1621 (7.4%) who gave a history or had the physical findings of heart disease (Table 1). These 1621 men were referred to the medical officers in the chest section, with the reason for doing so slipped on the bucksheet<sup>5</sup> that went along with each man. The leading cardiac causes for referral were (1) a history of heart trouble, physical findings absent, (2) tachycardia, (3) an elevation of blood pressure above 148/88, and (4) murmurs.

Only 226 (1%) had organic heart disease, however. This compares favorably with a study of 20,000 examinees in the Pacific Northwest by Wilburne and Ceccolini.<sup>23b</sup> They noted heart disease in 288 (1.44%), but their Selective Services examinees were 20 to 45 years of age, which accounts for the higher incidence. It is difficult to com-

pare my figures with others previously reported because mine are not based on the percentage of the total number of men rejected.

TABLE 1.—CARDIAC HISTORY AND FINDINGS AMONG 23,000 INDUCTEES AND VOLUNTEERS

	Number	Percentage
1. History, physical findings absent . . . . .	659	2.8
2. Tachycardia . . . . .	351	1.5
3. Hypertension . . . . .	327	1.4
4. Rheumatic heart disease . . . . .	203	0.9
5. Congenital heart disease . . . . .	20	0.1
6. Thyrotoxicosis . . . . .	32	0.15
7. Ventricular extrasystoles . . . . .	15	0.08
8. Luetic aortic insufficiency . . . . .	3	
9. Auricular fibrillation . . . . .	3	
10. Bradycardia (digitalis) . . . . .	2	
11. Bilateral splanchnicectomy (juvenile hypertension) . . . . .	1	
12. Lutembacher's syndrome . . . . .	1	
13. Postoperative myxedema . . . . .	1	
14. Hypothyroidism . . . . .	1	
15. Situs inversus . . . . .	1	
16. Pernicious anemia . . . . .	1	
Total referred . . . . .	1621	7.4
Total organic heart disease . . . . .	226	1.0

TABLE 2.—PERCENTAGE OF REFERRALS IN EACH OF THE GROUPS

	Number	Percentage
1. History, physical findings absent . . . . .	659	40.7
2. Tachycardia . . . . .	351	21.8
3. Hypertension . . . . .	327	20.3
4. Rheumatic . . . . .	203	12.4
5. Congenital . . . . .	21	1.3
6. Thyrotoxic . . . . .	32	1.9
7. Luetic . . . . .	3	0.1
8. Arrhythmias . . . . .	3	0.1
9. Miscellaneous . . . . .	23	1.4
Total . . . . .	1621	100.0

*History of Heart Trouble, Physical Findings Absent.* This was the largest and most difficult group with which the chest examiner had to contend. It has not been mentioned previously. Of the 23,000 examinees, 659 (2.8%) gave a history of heart trouble, but there were no cardiac findings. The most common story given by the examinee was that he had a "leakage of a valve" or a "murmuring of the heart," which had been found on a previous examination from 1 day to 37½ years earlier. The same held true for the complaints of an "athlete's" or enlarged heart, a rapid pulse, and high blood pressure. Sometimes the examinee used such terms as "tachycarditis," or "macrocarditis," or that he was treated for "blood pressure." Careful questioning along these lines usually brought out that he had been examined very infrequently, if at all, since the original findings. Some examinees made self-diagnoses because of symptoms generally attributed to heart disease or popularly thought to be due to hypertension. Any man with a history of acute rheumatic fever or of rheumatic heart disease, either during childhood or of more recent origin, which had confined him to bed for weeks or months, despite a lack of abnormal physical findings, was investigated further. It would have been

much easier to overlook many of these men who had cardiac complaints without findings, but the medical officers in the chest section requested that these men be referred to them for further examination. Such an inductee, who was reexamined carefully, had his morale boosted immeasurably by the thoughtfulness of the medical officer. Fully a third of the 1621 examinees who I weeded out of the line accepted the decision of the medical officers graciously. From the standpoint of the ultimate disposal of the inductee, the time taken for this group of men was of untold value. A man who complains constantly about his "heart trouble" is of no use, military or otherwise. If this percentage in the group under consideration was consistent for the nation,<sup>16c</sup> a total of 364,000 men gave a history of heart trouble but physical findings were absent. Probably the major accomplishment of the medical officers at the Armed Forces Induction Stations can be attributed to the wisdom of those in the chest sections in their handling of such a large group of complainants.

*Tachycardia.* The second important problem was the range of the pulse. MR 1-9 state that a truly persistent heart rate of 100 or over should be considered a cause for rejection. As emotion raised the pulse very easily, it had to be ruled out as a factor. All the more so at this station where the chest examination followed the interview with the neuropsychiatrist. Moreover, the heart rate is considered one of the poorest criteria of cardiovascular fitness.<sup>11a</sup> There were 351 men (1.5% of the 23,000 examinees and 21.8% of those referred) who had a tachycardia. The combination of a rapid cardiac rate and an elevated blood pressure on the initial examination in the sitting position was common. Tactful handling of the inductee was an important factor. Generally, if the rapid rate persisted, it was above 120 and other signs of neurocirculatory instability were present. No satisfactory relationship between the basal pulse rate, sitting pulse rate, and physical fitness for strenuous exertion in normal healthy young men has been noted.<sup>3</sup> Emotional factors were largely responsible for the high resting pulse rates commonly found during the pre-induction medical examination of such men. Brown<sup>4b</sup> stated that during the course of a 12 month period there were only 36 soldiers discharged from the Army at the Station Hospital, Fort Devens, Massachusetts because of organic heart disease. In the same period, however, there were 300 soldiers with the neurocirculatory syndrome at that hospital, nearly 10 times as many as those with organic heart disease. He felt that the presence of a large number of soldiers with neurocirculatory asthenia was a challenge to the examining physicians at the Induction Stations.

*Hypertension.* The third largest group were those with an elevated blood pressure. In a previous study<sup>9a</sup> I reported that hypertension was the most common cause of organic heart disease regardless of race or sex. MR 1-9, although setting a limit, allows freedom of interpretation and judgment above that limit.<sup>18</sup> A cause for rejection was a "persistent blood pressure at rest above 150 mm. systolic or above 90 diastolic, unless in the opinion of the medical examiner the increased blood pressure was due to psychic reaction and not secondary to renal

or systemic disease." There were 327 (1.4%) of the examinees who presented what is probably our most difficult cardiovascular problem. Wilburne and Ceccolini<sup>23a</sup> observed hypertension in 241 (0.96%) of 25,000 Army examinees, and suggested that the incidence is overestimated. The earliest report<sup>1</sup> on the incidence of hypertension among Selective Service registrants was 3.02%.

Opinions differ greatly as to the upper range of blood pressure readings, especially in younger men. White<sup>22a</sup> stated that under the excitement of the examination 160 might be acceptable as the upper limit of the systolic pressure, but he would not raise the diastolic level much above 90 if any. It is evident also that the blood pressure of hypertensives may be notoriously labile.<sup>6,7</sup> In the earliest work on hypertension, Janeway<sup>9b</sup> said he regarded with suspicion any pressure above 135 mm.; and 150 in a young person, when found on several examinations and with due precautions. Lewis<sup>12</sup> felt that values above 160 mm. Hg definitely surpass normal limits, while a diastolic pressure of 100 mm. is generally regarded as definitely abnormal. Russek's observations<sup>16</sup> indicate that a normal person may show little fluctuation in blood pressure in youth, and considerable variability in middle age. Rogers and Palmer<sup>14</sup> directed attention to transient elevations in blood pressure that are observed in men during physical examination for the Armed Forces. During 1 month at the Office of Naval Officer Procurement in Boston, they found 222 (14%) of 1574 applicants had mild variable hypertension at the initial examination; the systolic pressure varied from 140 to 160 mm., and occasionally higher, and the diastolic pressure ranged from 95 to 110 and rarely as high as 120. In Chicago<sup>8b</sup> the special board found that the hypertensives offered the greatest problem. Although this board adhered to the instructions in MR 1-9, it felt that it was here, if any place, that more liberality might have been shown. The New York<sup>11c</sup> reexamining board stated that the critical levels of systolic and diastolic blood pressure have not been established on a firm basis. However, they added that until further data are available or the need for manpower becomes acute, it would seem wise to adhere to the criteria at present in use, both because of possible future damage to the individual and because of danger of swelling the pension lists for disability.

On the initial cardiac examination in the sitting position many high readings were obtained, not only systolic but also diastolic, due mainly to emotional factors. I found that a few seconds of friendly chit-chat with the examinee, not only to put him at ease but also to bring back his feeling of individuality, and the taking of the blood pressure last, although the cuff was applied before auscultating the cardiac area, avoided many of the temporary high readings. After the psychic factor was handled, and the reading remained above 160 systolic and 100 diastolic on two or more consecutive estimations, then I considered the man a hypertensive. The majority of these men were neither aware of the elevated blood pressure nor did they have any of the psychoneurotic manifestations generally associated with known essential hypertension. This finding not only appears much earlier in life

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*Hypertension.* The third largest group were those with an elevated blood pressure. In a previous study<sup>9a</sup> I reported that hypertension was the most common cause of organic heart disease regardless of race or sex. MR 1-9, although setting a limit, allows freedom of interpretation and judgment above that limit.<sup>18</sup> A cause for rejection was a "persistent blood pressure at rest above 150 mm. systolic or above 90 diastolic, unless in the opinion of the medical examiner the increased blood pressure was due to psychic reaction and not secondary to renal

or systemic disease." There were 327 (1.4%) of the examinees who presented what is probably our most difficult cardiovascular problem. Wilburne and Ceccolini<sup>23a</sup> observed hypertension in 241 (0.96%) of 25,000 Army examinees, and suggested that the incidence is overestimated. The earliest report<sup>1</sup> on the incidence of hypertension among Selective Service registrants was 3.02%.

Opinions differ greatly as to the upper range of blood pressure readings, especially in younger men. White<sup>22a</sup> stated that under the excitement of the examination 160 might be acceptable as the upper limit of the systolic pressure, but he would not raise the diastolic level much above 90 if any. It is evident also that the blood pressure of hypertensives may be notoriously labile.<sup>6,7</sup> In the earliest work on hypertension, Janeway<sup>9b</sup> said he regarded with suspicion any pressure above 135 mm.; and 150 in a young person, when found on several examinations and with due precautions. Lewis<sup>12</sup> felt that values above 160 mm. Hg definitely surpass normal limits, while a diastolic pressure of 100 mm. is generally regarded as definitely abnormal. Russek's observations<sup>16</sup> indicate that a normal person may show little fluctuation in blood pressure in youth, and considerable variability in middle age. Rogers and Palmer<sup>14</sup> directed attention to transient elevations in blood pressure that are observed in men during physical examination for the Armed Forces. During 1 month at the Office of Naval Officer Procurement in Boston, they found 222 (14%) of 1574 applicants had mild variable hypertension at the initial examination; the systolic pressure varied from 140 to 160 mm., and occasionally higher, and the diastolic pressure ranged from 95 to 110 and rarely as high as 120. In Chicago<sup>8b</sup> the special board found that the hypertensives offered the greatest problem. Although this board adhered to the instructions in MR 1-9, it felt that it was here, if any place, that more liberality might have been shown. The New York<sup>11c</sup> reexamining board stated that the critical levels of systolic and diastolic blood pressure have not been established on a firm basis. However, they added that until further data are available or the need for manpower becomes acute, it would seem wise to adhere to the criteria at present in use, both because of possible future damage to the individual and because of danger of swelling the pension lists for disability.

On the initial cardiac examination in the sitting position many high readings were obtained, not only systolic but also diastolic, due mainly to emotional factors. I found that a few seconds of friendly chit-chat with the examinee, not only to put him at ease but also to bring back his feeling of individuality, and the taking of the blood pressure last, although the cuff was applied before auscultating the cardiac area, avoided many of the temporary high readings. After the psychic factor was handled, and the reading remained above 160 systolic and 100 diastolic on two or more consecutive estimations, then I considered the man a hypertensive. The majority of these men were neither aware of the elevated blood pressure nor did they have any of the psychoneurotic manifestations generally associated with known essential hypertension. This finding not only appears much earlier in life

than has been assumed, but it has a longer duration than it is generally thought to have.<sup>9c,d,e,f</sup> It must be emphasized that no applicant was rejected as the result of one or two blood pressure readings. When the estimation of the blood pressure was regarded as abnormal, or in case of doubt, the procedure was repeated twice daily (in the morning and in the afternoon) for a sufficient number of days (usually 3), which enabled the medical officers to arrive at a definite conclusion.

TABLE 3.—PERCENTAGE OF VALVULAR LESIONS IN RHEUMATIC HEART DISEASE

	Number	Percentage
Mitral . . . . .	152	74.8
Aortic . . . . .	15	7.4
Mitral and aortic . . . . .	36	17.8
Total . . . . .	203	100.0

*Rheumatic Heart Disease.* Although not strictly comparable because the men were 20 to 45 years of age, Wilburne and Ceccolini<sup>23b</sup> reported rheumatic heart disease in 183 (0.9%) of the 20,000 examinees in the Pacific Northwest. In their cases the mitral valve was involved alone in 152 (83.1%), the aortic valve only in 8 (4.4%), and combined mitral and aortic defects were observed in 23 (12.5%). I found 203 (0.9%) of the 23,000 examinees had organic heart disease on this basis. Disease of the mitral valve alone was noted in 154 (74.8%), aortic alone in 15 (7.4%), and combined aortic and mitral lesions were noted in 36 (17.8%).

The murmurs were the essential part of the picture. Only 48% of the 203 examinees gave a history of acute rheumatic fever and/or rheumatic heart disease. Among the remainder the valvular disease was diagnosed for the first time. The timing of the murmur was not as important as its character. A well-circumscribed, forceful apex beat, possibly with a palpable thrill, was suggestive of mitral stenosis, but not pathognomonic, even if noted outside of the left mid-clavicular line. The presence of these findings without a murmur was of no significance. Accentuated pulmonic sounds alone were entirely too common to be given much consideration. The variability of murmurs in mitral stenosis was first noted by Hope.<sup>9g,h,i</sup> In a study of 237 cases of this valvular lesion, I found that the murmurs were readily recognized by the characteristic rasping sound without resorting to definitely isolating the bruits in the cardiac cycle by timing.<sup>9j</sup> This must be borne in mind, for in a series of 835 recruits, Bramwell<sup>2</sup> noted signs simulating mitral stenosis, a duplicated second sound (generally associated with an apical systolic murmur) in 157, all of them acceptable for general service. Furthermore, it has been shown that there is no relationship between the character of rheumatic fever, the number of recurrences, and the age of the patient at the onset, on one hand, and the development of cardiac damage, on the other hand.<sup>4a</sup>

These difficulties were readily appreciated not only by the individual examiner, but also by the reexamining boards which were able to check the selected examinees carefully. The Boston board<sup>22b</sup> considered this one of their most difficult problems, as did the New York<sup>11c</sup> and the San Francisco<sup>10</sup> boards. The Philadelphia<sup>19</sup> board stated

that of the 160 men rejected for mitral insufficiency without cardiac enlargement, a great many did not have organic heart disease, but the loudness of the murmur in certain positions and following exercise caused rejection, because of the possibility that, if reclassified, they would be discharged from the service sooner or later. The Chicago<sup>8b</sup> board, however, reported that rheumatic heart disease offered no great difficulty except as far as the accuracy in the diagnosis of the lesion was concerned.

*Other Conditions.* Congenital heart disease was present in only 21 (0.1%) of the 23,000 examinees. This incidence may be compared with that of a previous study made at the Cook County Hospital<sup>21</sup> and that of Wilburne and Ceccolini,<sup>23b</sup> where it was the same.

*Comment.* There were a variety of other conditions, but only two require comment. Two men, who had bradycardia on the basis of digitalis, took the drug on their own volition as they had heard it was a good "heart tonic." No instance of malingering on this basis was found. The other point of interest was the finding of only 3 (Negro) men with syphilitic aortic insufficiency, despite the known incidence of syphilis among the examinees, 7% of whom were Negroes. This extremely low incidence of syphilitic heart disease, which averaged 13% among cardiacs at the Cook County Hospital<sup>9a</sup> in 1932 and 1933 when 30% of the patients were Negroes, can only be explained by the excellent treatment that most luetics receive, based on the modern public health program. Once aortic insufficiency appears in the young male syphilitic, the interval between the changes in the valve and the appearance of severe cardiac symptoms seems to be comparatively short.<sup>9a</sup> However, the Chicago<sup>8b</sup> reexamining board, the only one to comment on this, doubted that the true incidence of syphilitic heart disease among examinees is represented by even 0.5%.

It must be emphasized again that this is only the report of one among many civilian physicians who had the good fortune to be able to examine (23,000) inductees and volunteers. The figures given in this study are *not* the number or percentage of those rejected by the Armed Forces. We did accomplish our task, for the elimination of heart ailments was satisfactorily performed in enlistment, recruiting, induction, and training areas.<sup>17</sup>

*Summary.* While serving as a civilian physician on part-time temporary duty attached to a chest section of a medical unit at the Armed Forces Induction Station in Chicago, I examined 23,000 inductees and volunteers between the ages of 17 and 38 years. Although these were routine initial cardiac examinations, with an average of 3 minutes to each examinee, the results, when compared with other reports of a somewhat similar nature, seem fairly accurate. There were 1621 men (7.4%) who had a history and/or physical findings of heart disease, but only 226 (1%) had organic heart disease.

The largest group was those with a history of heart trouble, physical findings absent, 659 (2.8%). The second largest number was those with tachycardia, 351 (1.5%); third, hypertension in 327 (1.4%), and the fourth, those with rheumatic heart disease, 203 (0.9%).



Outstanding was the wisdom and tact displayed by the medical officers in the chest section in the handling of all inductees or volunteers who complained of any symptoms relating to or indicative of heart trouble, for the ultimate benefit of both the Armed Forces and the individual.

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## ACUTE SYPHILITIC MENINGITIS

## A DISCUSSION OF THE PROBLEMS ENCOUNTERED IN THE DIAGNOSIS

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A SMALL proportion of all persons infected with syphilis develop an acute meningitis as the result of an active infection of the meninges by

the *Treponema pallidum*. The diagnosis of this form of syphilis is often difficult. Among 9 cases of acute syphilitic meningitis seen at this hospital during the past 2 years, 5 presented perplexing clinical or laboratory manifestations. It is the purpose of this paper to report these sources of diagnostic error.

Although treponemal invasion of the neuraxis in early syphilis is a frequent occurrence,<sup>6</sup> the production of symptoms of acute meningitis is uncommon. Only 55 of Moore's 2675 cases of early syphilis developed this condition,<sup>9</sup> and reports in the literature usually consist of a relatively small number of cases observed over a period of years.

Acute syphilitic meningitis is most often the result of inadequate treatment, appearing as a relapse phenomenon or neurorecurrence, but occasionally it develops early in the course of luetic infection without previous treatment.

Although pathologically there is a widespread meningeal involvement in all cases of luetic meningitis, the clinical manifestations fall largely into one of three groups. The first consists of basilar meningeal signs, predominantly cranial nerve palsies. The second group is characterized by symptoms referable to the cerebral vertex, such as hemiplegia, aphasia, convulsions or delirium. The third group of patients have all the signs of acute hydrocephalus with headache, nausea, vomiting and choked disks. The occurrence of increased intracranial pressure in this latter group is presumably due to an obstruction of the spinal fluid circulation in the posterior fossa.

The symptoms exhibited by our 9 patients fell into one of these three groups with surprisingly little overlapping or admixture. Each of our patients had early syphilis, usually less than a year's duration. The spinal fluid findings in our cases were similar to those reported in the literature and consisted usually of an increased pressure, pleocytosis, increased protein, and almost always a positive Wassermann test. Since excellent reports on the clinical and laboratory manifestations of this condition have appeared in recent years,<sup>8,9,11,13</sup> only the cases which illustrate certain unusual features will be discussed.

**Relation of Syphilitic Meningitis to Previous Treatment.** In Merritt and Moore's review on the subject<sup>8</sup> they found only a rare case of acute syphilitic meningitis developing while the patient was taking standard antiluetic treatment. Occasionally the syndrome has been observed to appear during mercury inunction, but its occurrence during bismuth treatment is unusual. In fact, the use of bismuth has been generally thought to protect the patient against neurorelapse.<sup>10</sup> It was for this reason that the diagnosis of acute syphilitic meningitis in 2 of our cases was delayed, both of them having been under bismuth therapy at the time they developed symptoms.

**Case Studies.** CASE 1. F. J., a 21 year old white girl, was first found to have syphilis in April 1943, when she went to a physician with a generalized skin eruption. The serologic test for syphilis was positive and antiluetic therapy was started with disappearance of the cutaneous lesions. She received 14 weekly injections of neoarsphenamine followed by 8 weekly intramuscular injections of a soluble bismuth preparation. During the course of bismuth therapy she noted the appearance of a headache, which became so severe

that treatment was stopped and the patient remained in bed. Nausea and vomiting, blurred vision, dizziness and tinnitus then developed. All these symptoms became progressively worse and she finally sought hospital admission 8 weeks after their onset.

On admission to the hospital in December 1943, the patient appeared obviously ill, irritable but coherent. There was considerable stiffness of the neck, but the Kernig and Brudzinski signs were negative. The chief neurologic manifestation was a choking of both optic disks. These showed approximately 2 diopters of papilledema with some retinal edema and venous congestion. There were numerous areas of old choroidal pigmentation in both fundi. The other cranial nerves were not affected, the reflexes were normal, and sensory examination was also normal. The heart, lungs and abdomen showed no abnormalities.

The leukocyte count was 5500 per c.mm., and the differential count was normal. The Kahn test of the blood was positive with 200 Kahn units. The spinal fluid contained 286 cells, all lymphocytes, and 285 mg. of protein per 100 cc. The spinal fluid sugar was 59, and the chlorides 640 mg. per 100 cc. The mastic curve was 45554 and the spinal fluid Kahn was positive. Repeated spinal fluid examinations showed essentially the same values with a consistently positive Kahn test.

*Course.* The oral temperature on admission was 98° F., but fluctuated between 98° and 99.5° F. during the hospital stay. The patient continued to complain of headache until mapharsen therapy was begun on the 6th hospital day. Following the third daily injection of 60 mg. of mapharsen, the patient's temperature became normal and her headache was almost completely relieved.

She received daily injections of mapharsen for 7 days and was then placed on tri-weekly injections of mapharsen for 10 weeks. After 5 weeks the papilledema had disappeared, but no change in the chorioretinitis was observed. After 10 weeks of treatment the spinal fluid contained 4 cells, 38 mg. of protein per 100 cc. and a mastic of 431111. The spinal fluid Kahn was positive and the Wassermann was also positive, using 0.0625 cc. of fluid.

CASE 2. J. B., a 28 year old colored female, developed a generalized skin eruption in August 1942, 1 month after marriage. The serologic test for syphilis, which had been negative in June 1942, was found to be positive in October 1942, and antiluetic treatment was begun. Fifteen regular weekly injections of an arsenical compound and 4 injections of an oil suspended bismuth preparation had been given when the patient was forced to stop treatment because of severe headache in January 1943. This was followed during the next few weeks by paresthesias over the right side of the face, deafness of the right ear, tinnitus, nausea and vertigo. She also noted that her mouth drooped on the right side, that she could not close her right eye, and that her smile was "crooked." The headache became progressively worse and she finally was admitted to the hospital in March 1943.

On admission the patient appeared to be a well-nourished Negress, not acutely ill, but complaining of severe headache. The pupils reacted well to light and accommodation and the extraocular movements were normal. The fundi were negative with normal physiologic cupping of the optic disks. There was definite hypesthesia of the right side of the face with weakness of the forehead and facial muscles on the right side. Considerable deafness was present on the right. The tongue protruded in the midline. The neck was not stiff and the lungs were clear. No abnormality was found in the heart and the blood pressure was 140/90. The abdomen was normal, but examination of the rectum revealed a dense stricture 7 cm. above the anus. The deep reflexes were normal, and no sensory disturbances or motor weaknesses of the extremities were noted.

The white blood cells totalled 6100 per c.mm. (neutrophils 61%). The Kahn test of the blood was positive. The spinal fluid was clear and contained 700 white blood cells per c.mm., 82% of which were lymphocytes. The total protein was 80 mg. per 100 cc. and the spinal fluid Kahn was positive.

*Course.* The patient's temperature remained below 99° F. during the entire hospital stay and she improved rapidly with complete recovery from the cranial nerve lesions, without any specific treatment. Following discharge from the hospital, she received 19 injections of mapharsen and 15 of bismuth subsalicylate. In January 1944 the spinal fluid contained no cells, showed a negative mastic, and had 16 mg. of protein per 100 cc., but gave a positive Wassermann in 0.5 cc. of spinal fluid.

Since acute syphilitic meningitis rarely occurs during active anti-luetic treatment, the diagnosis of a lymphocytic meningitis which develops during therapy as luetic should be made with extreme caution. Such a diagnosis, however, seems justified in the above 2 cases, because the syphilitic infection was only of several months' duration, and because of the persistence of a positive spinal fluid Wassermann long after other signs of the meningitis had disappeared.

In the first case, the patient was treated with a soluble bismuth compound at the time of onset of the meningeal symptoms. Such preparations of bismuth are rapidly excreted, usually in 48 hours, and when given weekly for cases of early syphilis, constitute inadequate treatment. Although this would explain the appearance of meningitis in the first case, its occurrence in the second patient who received standard treatment is more difficult to understand. Merritt<sup>8</sup> explained such cases as being the result of inadequate treatment for that particular individual, but even the relatively intensive 26-week Army schedule may not protect the patient against developing meningitis.<sup>3</sup>

**Papilledema in Syphilitic Meningitis.** The occurrence of a severe papilledema in acute syphilitic meningitis has frequently resulted in diagnostic errors. It is easily understood how the presence of choked disks together with other signs of increased intracranial pressure, such as headache, nausea and vomiting, can lead to consideration of an intracranial tumor as the most likely diagnosis. Although these signs of acute hydrocephalus have been repeatedly observed in luetic infections,<sup>1,4,5</sup> they still remain a source of confusion. The following patient, who developed such symptoms after a head injury, is an example of this type of problem.

**CASE 3.** M. J., a 22 year old white female, had been under treatment for early syphilis for 4 months prior to admission and had received regular weekly injections of neocarsphenamine. Eleven days after the last injection, she developed a headache and 2 days after this sustained an injury to the forehead in an automobile collision. This resulted in no loss of consciousness, but in an apparent aggravation of the headache. The patient developed tinnitus and dizziness and noted transitory numbness of the upper extremities. Three weeks after the onset of the illness, her neck became stiff and painful on motion. The headaches became more severe and nausea and vomiting developed.

Because of the emphasis the patient placed on her head injury she was admitted to the surgical service of Grady Hospital with a provisional diagnosis of a subdural hematoma. On admission the patient appeared apathetic but cooperative, and in no obvious distress. There was a definite bilateral papilledema of 1 to 2 diopters. The retinal veins appeared distended in both fundi. There was a mild right-sided facial weakness with some impairment of hearing on the right. The neck was moderately stiff with a positive Brudzinski sign. The heart, lungs and abdomen were negative. The deep reflexes were normal.

Examination of the urine showed nothing abnormal. There were 14 gm. of hemoglobin per 100 cc. of blood, and the leukocyte count was 15,000 per

c.mm. The blood Kahn was positive. The spinal fluid contained 1460 white cells per c.mm., 98% of which were lymphocytes. The spinal fluid protein level was 200 mg. per 100 cc., and the mastic curve was 13331. The spinal fluid Kahn was repeatedly positive.

*Course.* After the spinal fluid findings were obtained, the patient was transferred to the medical ward. During the first week in the hospital the temperature fell from 102 to 99° F., and the headache cleared considerably although no treatment was instituted. During the second week, mapharsen was given twice weekly with no appreciable change in the patient's symptoms. The headache continued, with some stiffness of the neck, but after 6 weeks she became symptom-free and was discharged. Four months after the onset of the illness, a repeated spinal fluid examination showed 44 mg. of protein per 100 cc., a mastic curve of 442100 and a positive Kahn. The papilledema had completely disappeared and the patient felt completely well.

Recognition of the luetic nature of this patient's illness was obscured by the patient's emphasis upon her head injury. She at first dated all the symptoms to her trauma, and it was only after the spinal fluid report had returned that further questioning brought to light her luetic background and the fact that the symptoms preceded the injury by a few days.

**Response of Syphilitic Meningitis to Specific Treatment.** One of the most frequently used aids in the diagnosis of acute syphilitic meningitis has been the response to antiluetic therapy. That this criterion may be of little value is evident in Cases 2 and 3, where marked clinical improvement occurred without any specific treatment. In such patients the results of arsenical and bismuth therapy may easily be misinterpreted. Occasionally, however, a definite response to specific treatment can be observed, thus confirming the diagnosis of syphilis. The following patient is an example of the value of a therapeutic trial of mapharsen.

**CASE 4.** P. C., a 23 year old white female, entered the hospital in November 1943 in a completely irrational and stuporous condition. The history revealed that she had become ill 4 weeks prior to admission with a severe frontal headache. This became progressively worse and was associated with nausea, vomiting and earache. The patient consumed large quantities of headache powders for the pain and was also given sulfathiazole without relief. She complained of stiffness of the neck, became very irritable and occasionally lapsed into delirium for periods of 24 hours or more. Two days before admission she became stuporous and was finally admitted in this condition.

It was later revealed that the patient had begun weekly injections, presumably for syphilis, from a private physician several months prior to admission, but received only 4 treatments before becoming delinquent.

On admission the patient's temperature was 103° F. She appeared acutely ill, was irrational, and complained hysterically of headache. The pupils reacted well to light and accommodation. The fundi showed definite edema of the nerve heads bilaterally with some distention of the retinal veins. The other cranial nerves appeared intact. The nose and throat were normal and the neck quite stiff with a positive Brudzinski sign. The chest and heart were normal, the blood pressure 130/70, and the abdominal examination negative. The reflexes of the extremities were active; a bilateral Kernig sign was present.

Examination of the urine was negative. There were 12 gm. of hemoglobin per 100 cc. of blood, with 20,000 white blood cells per c.mm. (97% neutrophils). The blood bromide level was 125 mg. per 100 cc. and the blood Kahn positive. The spinal fluid contained 670 white blood cells per c.mm., 92%

of which were lymphocytes. The spinal fluid protein content was 200, the chloride 670, and the sugar 52 mg. per 100 cc. The mastic curve was 455551 and the spinal fluid Kahn was positive. Five subsequent spinal punctures revealed essentially the same results with only a small reduction of cells and protein before discharge.

*Course.* On admission the patient was thought to have meningococcal meningitis and received sulfadiazine with parenteral fluids. In 36 hours the temperature became normal and remained so. She became rational, had less stiffness of the neck and seemed to be remarkably improved. There appeared to be a slight weakness of lateral deviation of the right eye, which cleared in a few days. At the end of the first hospital week it became apparent that the patient had not completely recovered. She complained bitterly of headaches, became irritable and difficult to placate. She cried easily, had numerous aches and pains and was quite fretful. The spinal fluid findings remained the same as on admission, and on the 12th hospital day she was started on daily injections of mapharsen. After the third dose she obtained complete relief from her headache, became cheerful and, except for visual blurring, was entirely asymptomatic. A total of 20 mapharsen and 10 bismuth injections were given in the next 4 weeks, but the patient again became delinquent and has not returned.

In this case there appeared to be some improvement coincident with hydration, bromide excretion and sulfadiazine therapy, but it was not until mapharsen was given that the patient became well.

Not only will cases of syphilitic meningitis improve frequently without treatment, but other types of lymphocytic meningitis may get well coincidentally with antiluetic treatment. The course of virus meningitides, for example, is usually quite benign, and the patient may get well at the time he is receiving luetic therapy. In these instances the therapeutic response may be completely misinterpreted. Since syphilitic meningitis is not a rapidly fatal condition, it seems advisable to withhold treatment in undiagnosed cases of lymphocytic meningitis, unless the patient is very ill, in which case a therapeutic trial with mapharsen is justified.

**Relation of Meningitis of Spinal Fluid Tests for Syphilis.** It has now become well known that a positive spinal fluid Wassermann reaction in a patient with meningitis and systemic syphilis is not diagnostic of neurosyphilis, as an increase of protein in the spinal fluid may carry with it serum reagin.<sup>7</sup> It was for this reason that in the above patients a diagnosis of acute syphilitic meningitis could not be made simply on the basis of positive spinal fluid Wassermann or Kahn tests.

In a highly syphilitic population, therefore, falsely positive spinal fluid Wassermann tests become a not infrequent occurrence. There have been several cases at the Grady Hospital of tuberculous meningitis with persistently positive Wassermann tests and also 1 case of probable choriomeningitis which showed a similar reaction.\*

\* Since this paper was submitted for publication, a report on biologic falsely positive spinal fluid Wassermann reactions has appeared (Scott, V., Reynolds, F. W., and Mohr, C. F.: *Am. J. Syph. Gonorr. and Ven. Dis.*, 28, 431, 1944). This study showed that falsely positive spinal fluid Wassermann tests may occur in syphilitic and non-syphilitic patients during the course of pyogenic, aseptic, and tuberculous meningitis, and perhaps in other types of intracranial disease. These authors caution against making the diagnosis of neurosyphilis unless repeated spinal fluid examinations, performed after the acute infection has subsided, show the continued presence of reagin.

**Falsely Negative Tests.** Not only are falsely positive spinal Wassermann tests seen in non-luetic meningitides, but occasionally falsely negative tests occur in syphilitic meningitis. Extreme caution must be exercised in diagnosing this condition and the following case, which finally developed a positive spinal fluid Kahn after previously negative tests, is an example of this condition.

**CASE 5.** J. C., a 19 year old colored male, developed a penile lesion in September 1943, associated with a positive serologic test for syphilis. He was then treated with 5 mapharsen injections before becoming delinquent. Early in November 1943, he began having frontal headaches, which gradually became more severe. He noted associated nausea, vomiting and dizziness and was seen in the Out-Patient Department on Dec. 7, 1943. At this time physical examination showed a somewhat lethargic patient with no stiffness of the neck or cranial nerve palsies. The spinal fluid was reported as containing no cells, but since the fluid had been allowed to stand overnight, this count was not deemed accurate. There were 88 mg. of protein per 100 cc. of spinal fluid, the mastic was 110000, and the spinal fluid Kahn test was negative at both the state and hospital laboratories. It was unfortunate that a Wassermann test on the spinal fluid was not done at this time as it may have suggested the correct diagnosis. The patient again became delinquent and did not return until Jan. 17, 1944, when he was admitted to the hospital because of persistent headache, malaise and weakness.

On admission, the physical examination was entirely normal except for a moderate degree of lethargy. No neurologic abnormalities were noted. There were 14 gm. of hemoglobin per 100 cc. of blood, and the leukocyte count was 10,000 per c.mm. The spinal fluid contained 220 cells per c.mm., all lymphocytes, 128 mg. of protein per 100 cc., and the mastic curve was 331000. The spinal fluid Kahn test was now positive and the Wassermann was also positive with 0.125 cc. of spinal fluid.

**Course.** The patient's temperature never rose above 99° F. and he became completely asymptomatic after the first injection of mapharsen. He was then placed on a tri-weekly schedule of mapharsen and after 10 weeks the spinal fluid was again examined. This time there were 4 cells, 42 mg. of protein per 100 cc., the Kahn and mastic tests were negative, but the Wassermann was positive with 1 cc. and 0.5 cc. of spinal fluid.

Cases of syphilitic meningitis with negative spinal fluid Wassermann tests have been reported,<sup>8,12</sup> but such diagnoses often leave room for doubt. The above case is of interest therefore, because a positive spinal fluid Kahn finally appeared 6 weeks after negative tests had been obtained in the active stage of the illness. It is well known that the spinal fluid Kahn and Wassermann tests are the last of the spinal fluid tests to become positive in early neurosyphilis.<sup>2</sup> In this case apparently insufficient time had elapsed for a positive flocculation test to develop at the time of the first spinal puncture, even though the patient had meningeal symptoms. With the development of a higher protein level and a first zone colloidal reaction, the Kahn became positive and the diagnosis was established.

In cases such as this, when the spinal fluid Wassermann reaction is negative, a definite diagnosis of syphilitic meningitis can only be established by withholding treatment until the test becomes positive. In the milder cases of meningitis such a practice seems advisable. After the diagnosis has been made, it can be confirmed by repeated examinations of spinal fluid during syphilitic treatment. In meningitis of

luectic origin the cells, protein and mastic usually return to normal levels before the Wassermann reaction becomes completely negative.

**Summary.** During the past 2 years we have observed 9 cases of acute syphilitic meningitis, 5 of which presented diagnostic difficulties.

Despite the rarity of its occurrence, 2 cases of luectic meningitis appeared during the course of regular bismuth therapy.

Several of our patients with this syndrome responded without syphilitic treatment. Since other types of lymphocytic meningitis may improve coincidentally with specific therapy, a therapeutic response to arsenicals is usually of little value, though at times helpful in the diagnosis of acute syphilitic meningitis.

In 1 case of syphilitic meningitis in which there was a history of head trauma, the presence of papilledema was the source of diagnostic error.

In the highly syphilitic population of this region, falsely positive spinal fluid Wassermann tests are not infrequently observed in lymphocytic meningitides. One case of syphilitic meningitis is reported in which a negative spinal fluid test for syphilis appeared after the onset of clinical symptoms. Withholding treatment in such cases seems advisable in order to establish a definite diagnosis of luectic meningitis.

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## JOINT DISEASE ASSOCIATED WITH ACROMEGALY\*†

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ALTHOUGH Pierre Marie's<sup>6</sup> masterly description of the hypertrophic skeletal changes in the syndrome he named acromegaly was published

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in 1886, nearly half a century elapsed before acromegalic joint lesions became the subject of histologic investigation. To be sure, Llewellyn<sup>4</sup> in 1909 and Oppenheim<sup>5</sup> in 1913 noted gross alterations "similar to arthritis deformans" in the articulations of such patients. However, it remained for Erdheim<sup>2,3</sup> in 1931 to direct attention to the relationship between pituitary tumors and a specific form of articular disease. Unquestionably, the fact that the joint lesions in long-standing acromegaly may be indistinguishable from those of degenerative joint disease<sup>1</sup> delayed the recognition of their specific nature, as was pointed out by Erdheim. In this relatively uncommon syndrome, the amount of autopsy material suitable for the demonstration of early articular changes is small. Insofar as we could ascertain there are no reports of such cases in the English literature. Having had the opportunity to make such postmortem examination of the tissues from an acromegalic who died with bacterial endocarditis, we wish to report the pertinent findings, in order to substantiate Erdheim's thesis in part as well as to stimulate interest in this unusual arthropathy.\*

**Case Summary.** A 58 year old, male, Jewish photo-engraver entered the hospital complaining of severe low back pain of 8 weeks duration. Twenty years before admission, gradual and painless enlargement of the acral parts had begun, but for the last 15 years no appreciable change had taken place. Two months prior to entry, without known cause, the knees became tender, painful on motion and swollen. A severe, dull, bifrontal headache developed soon after and persisted constantly for several days. Within a week there appeared again without any obvious precipitating factor a sharp pain in the back centered in the midline below the scapular angle and extending a few inches to either side. Two weeks preceding admission both legs showed dependent edema. The patient had had moderate polydipsia and nocturia for many years. During the recent illness, he had been orthopneic and had lost about 30 pounds. Over 15 years before entry, he fractured both wrists. The remainder of the personal history was negative for symptoms of previous articular or cardiac disease. The marital and family histories were not remarkable.

Physical examination showed a poorly nourished, weak, elderly male with pronounced acromegalic features and skeletal changes (Figs. 1 and 2). There was no lymphadenopathy. The hair was normal except for frontal baldness. There were no tophi. A few remaining lower teeth showed caries. The mandible, nose and supra-orbital ridges were prominent and multiple exostoses could be palpated over the occiput. There was diffuse tenderness over the skull bones. The conjunctivæ were reddened but showed no petechiæ. Arcus senilis was marked. Both optic disks had indistinct margins and could be visualized only with a -20 lens. The visual fields were normal. The ears were long, the tongue thick, speech clumsy, voice deep. Distinct beading of the costochondral junctions was noted in the barrel-shaped chest. There was enlargement of the right breast. The heart was not definitely enlarged to physical examination,  $P_2$  was louder than  $A_2$ , and a blowing systolic murmur was heard diffusely over the precordium. The peripheral vessels were non-resilient, the blood pressure was 120/65. The lungs were hyperresonant, but at both bases dullness and moist râles were noted. The abdomen was markedly scaphoid, the spleen enlarged. Genitalia and prostate were normal.

The spine showed an increase in the cervical and thoracic curves, moderate rigidity and pain on motion. There was tenderness over the spinous processes

\* The authors wish to express their appreciation to Dr. Herman L. Blumgart, Physician-in-Chief, Beth Israel Hospital, Boston, for the permission to present the clinical material incorporated in this report.

of the 11th thoracic to the 4th lumbar vertebræ, greatest at the 12th dorsal. The hands and feet were large and spade-shaped and all peripheral joints showed evidence of marked hypertrophic changes. There was wasting of the musculature of the extremities, pitting edema of both lower legs and eczema about the left ankle. Knee jerks and ankle jerks could not be elicited. Neurologic examination was otherwise non-contributory.

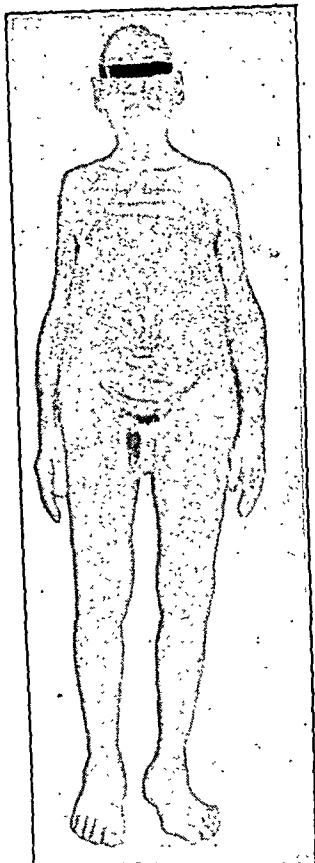


FIG. 1

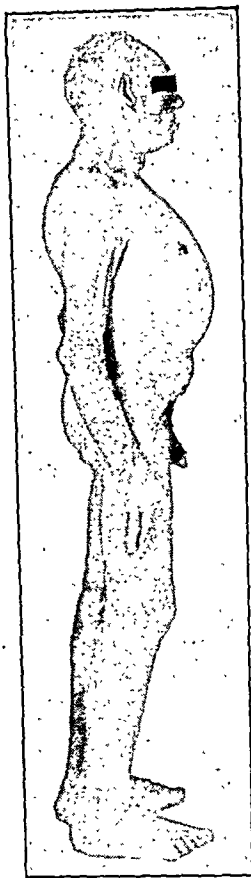


FIG. 2

FIGS. 1 and 2.—The pronounced acromegalic features and skeletal changes exhibited by this patient are well illustrated in these two photographs.

Roentgenograms of the chest revealed emphysematous lungs, tortuosity of the aorta, slight enlargement of the left ventricle and moderate scalloping of the ribs. Films of the skull showed the sella turcica to be enlarged with thinning and slight erosion of the posterior clinoid processes. Roentgenograms of the joints demonstrated flattening of the head of the right humerus, narrowing of the right humeral scapular articulation, widening of its glenoid process and increased density of subchondral bone alternating with cystic areas. Marked marginal hypertrophic changes were observed in the carpal and terminal phalangeal articulations. The intervertebral articulations and vertebral bodies in the dorsal segment of the spine showed massive spur formation. The 6th and 7th thoracic vertebræ had a wedge-shaped appearance and the intervening disk was collapsed in a manner suggesting an old fracture. Laboratory tests showed a diabetic type of glucose tolerance curve; basal metabolic rate up to +57%, not changed after administration of iodine; and a high normal value for urinary calcium by the Sulkowitch test. The serum calcium was 10 mg. per 100 cc., phosphorus 3 mg. per 100 cc. and phosphatase 7.6 units per 100 cc.

The course in the hospital was characterized by rapidly progressive generalized weakness, and irregularly elevated temperature to 102.5° F. in the presence of a low normal white blood cell count and a normal differential. The sedimentation rate was elevated. There was increasing evidence of systemic infection. A loud blowing aortic diastolic murmur appeared while the patient was under observation. Repeated blood cultures were positive for non-hemolytic streptococci. The patient did not respond to sulfonamide therapy and multiple transfusions. He developed microscopic hematuria, the non-protein nitrogen rose from 25 to 51 mg. %, the respirations became extremely labored and irregular and the patient died on the 47th day after admission.

*Pathologic Examination.\** A striking diminution in fatty tissue was noted in the subcutaneous tissues, omentum, mediastinum and all perivisceral areas. In its place, abundant connective tissue of unusual, gelatinous appearance was observed.

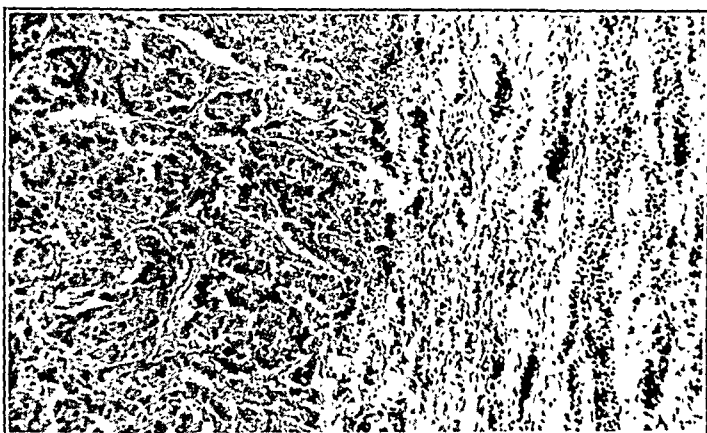


Fig. 3.—The structural and cytologic features of the pituitary adenoma are shown at the left of this photomicrograph ( $\times 85$ ). A margin of the compressed and atrophied gland is shown on the right-hand half of the reproduction.

Apparently due to the kyphoscoliosis of the spine, there had been moderate dextro-rotation of the heart, which was normal in shape but showed hypertrophy of the myocardium and weighed 410 gm. There were many areas of patchy atherosclerosis of the coronary vessels but no occlusions could be seen. The aorta exhibited several atheromatous plaques. Microscopically, the mitral, aortic and tricuspid valves showed changes characteristic of old rheumatic infection. On the mitral and aortic valves were superimposed vegetations consisting of massive clumps of cocci, leukocytes, red blood cells and fibrin and extending deeply into the valve structure. No Aschoff bodies were seen anywhere in the heart. Postmortem culture from the right auricle showed non-hemolytic streptococci and *Staphylococcus albus* after 2 days incubation.

Examination of the lungs gave evidence of moderate congestion and changes consistent with patchy pneumonitis in the right lower lobe. The spleen, weighing 440 gm. was of slightly increased firmness, and showed hyalinization of the centers of some follicles and intimal sclerosis of the larger vessels. The liver weighed 1760 gm. The parenchyma was normal except for moderate congestion about the central veins. The pancreas and kidneys appeared normal. The adrenal glands were slightly enlarged and showed moderate postmortem degeneration of the medullary portion and congestion of the cortex. The prostate gland was markedly enlarged. Its acini were increased

\* We are indebted to Dr. Monroe J. Schlesinger of the Beth Israel Hospital for all pathologic interpretations, except for those pertaining to the skeleton, which he kindly placed at our disposal.



FIG. 4.—Roentgenogram of an excised portion of the spine. Note the marked marginal lipping. The obliteration of the intervertebral disks between the 6th and 7th thoracic vertebrae could be the result of trauma.

in number and of irregular size and shape. They were lined by fairly tall columnar epithelium with basally placed, deeply staining nuclei. The epithelium appeared thrown up into folds, and the intervening fibromuscular material was relatively reduced in amount. The testes showed normal glandular structure and evidence of active spermatogenesis. The thyroid and parathyroid glands exhibited no definite pathologic features. The vocal cords were not remarkable. The dura appeared slightly thickened and edematous. The contents of the cranial vault were not remarkable except for findings relating to the hypophysis.



FIG. 5.—The pronounced widening and irregular ossification of the costochondral junctions are illustrated in these roentgenograms of representative segments.

The enlarged pituitary gland, weighing in excess of 4 gm., projected from the bony fossa. It was found to consist of a well-defined adenomatous nodule surrounded by a fibrous tissue capsule and composed of nests and anastomosing cords of cells in a richly vascular stroma, with ample fibrous interstitium (Fig. 3). The cells were rather large, irregularly rounded and had poorly demarcated borders, a pale pink, finely granular cytoplasm and large, centrally and eccentrically placed, oval, vesicular nuclei, each containing eccentric nucleoli. There were no active mitoses or giant cells. The predominant cellular constituents exhibited an only imperfect resemblance to the eosinophilic cells of the pituitary gland and possessed a cytoplasm which was more granular and more deeply staining than that of the chromophobe cells. At the periphery of the adenomatous nodule, a compressed but otherwise fairly normal appearing anterior lobe was seen, containing preponderantly chromophobe elements but also some poorly staining eosinophilic cells. A small piece of intermediate lobe showed cells whose arrangement tended to be in the form of acini. An occasional dilated acinus was filled with bluish-pink staining material similar in appearance to colloid. An antemortem biopsy specimen from the right breast revealed changes typical of gynecomastia.

There was prominent lateral and slightly less conspicuous anterior lipping of the vertebral bodies at the margins of the disks. The intervertebral cartilages were flattened. The 6th and 7th segments of the thoracic spine were completely fused (Fig. 4). Segments of rib showed well-defined fusiform enlargement of the costochondral junctions (Fig. 5).



FIG. 6.—In this roentgenogram of an excised portion of the femoral condyles of the left knee are shown the hypertrophic changes of advanced degenerative joint disease.



FIG. 7.—Marked bony overgrowth (lipping) about an expanded intervertebral disk. These changes, although very pronounced, are apparently similar to the spinal lesions that are frequently seen in elderly non-acromegalic subjects.

Grossly, the right knee joint showed an extraordinary degree of cartilaginous and bony overgrowth at the perichondral margins (Fig. 6). The articular aspects of the patella and the patellar surfaces of the femur were strikingly irregular. The hyaline covering deeply eroded, the subchondral bone had become exposed on the weight-bearing portions of the femoral condyles. The synovial lining tissue had undergone pronounced villous hypertrophy and, in the fresh state, appeared markedly hyperemic.

Microscopic sections of the intervertebral articulations revealed marked anterior protrusion of the disks and evidence of a severe cataplastic process involving the annulus fibrosus, nucleus pulposus and the cartilaginous plates (Fig. 7). Fibrillation of the hyaline substance, clustering of chondrocytes and mucinoid degeneration of the disk centers with marked fibrosis in the peripheral areas were apparent. Frequent focal deposits of calcium and occasional vascularization extending from the marrow through the calcified layer could be observed. The 5th and 7th disks were greatly narrowed (Fig. 4), and the anterior margins of the vertebral bodies exhibited prominent beak-shaped bony overgrowths, occasionally almost enveloping the protruding disk material. The 6th intervertebral disk had nearly disappeared, leaving only a few circumscribed cartilaginous masses between the bony borders of the adjacent vertebrae.

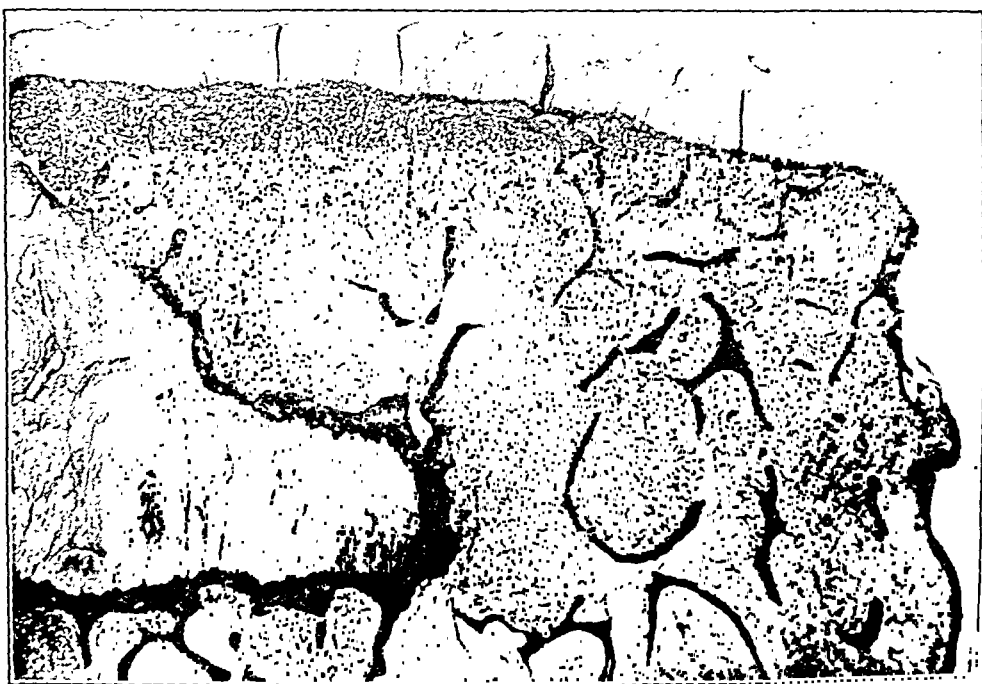


FIG. 8.—An extremely marked marginal overgrowth of bone ( $\times 8$ ) of one margin of the patellar surface of the femur. Pronounced degenerative changes in the articular cartilage are readily seen.

In some regions, patches of condensed, newly formed bone were visible, indicating an active growth process resembling that of a healing fracture. Throughout the sections, wide osteoid seams were noted and tongues of proliferating cartilage frequently extended through the calcified layer into the marrow spaces. Transverse sections of the vertebral bodies and intervertebral articulations from T8 to L2 demonstrated similar alterations. The marginal lipping, however, was more pronounced in the thoracic region than in the lumbar segments and had reached large proportions on the lateral aspects of the vertebrae (Fig. 4).

Sections from the patella, the patellar surface of the femur and from the medial and lateral femoral condyles showed an extreme degree of degenerative change, with cartilaginous and bony hypertrophy (Figs. 8 and 9). Overgrowths at the perichondrial margins measured as much as  $2 \times 3$  cm. and widely overhung the periphery of the cortex. The articular cartilage was markedly fibrillated, the matrix being roughly cleft. The chondrocytes had undergone degenerative and proliferative changes in all layers. The weight-

bearing surfaces of the condyles were, in large areas, made up of condensed subchondral bone devoid of any cartilaginous covering. The synovial membrane of the knee joint was characterized by hypertrophy of the villi which showed a notable increase in fibrous tissue (Fig. 10). Infiltration with chronic inflammatory cells was not a striking feature. A frequent finding in sections from bone marrow and synovialis were large areas of myxomatous degeneration in the fatty and connective tissues (Fig. 10).

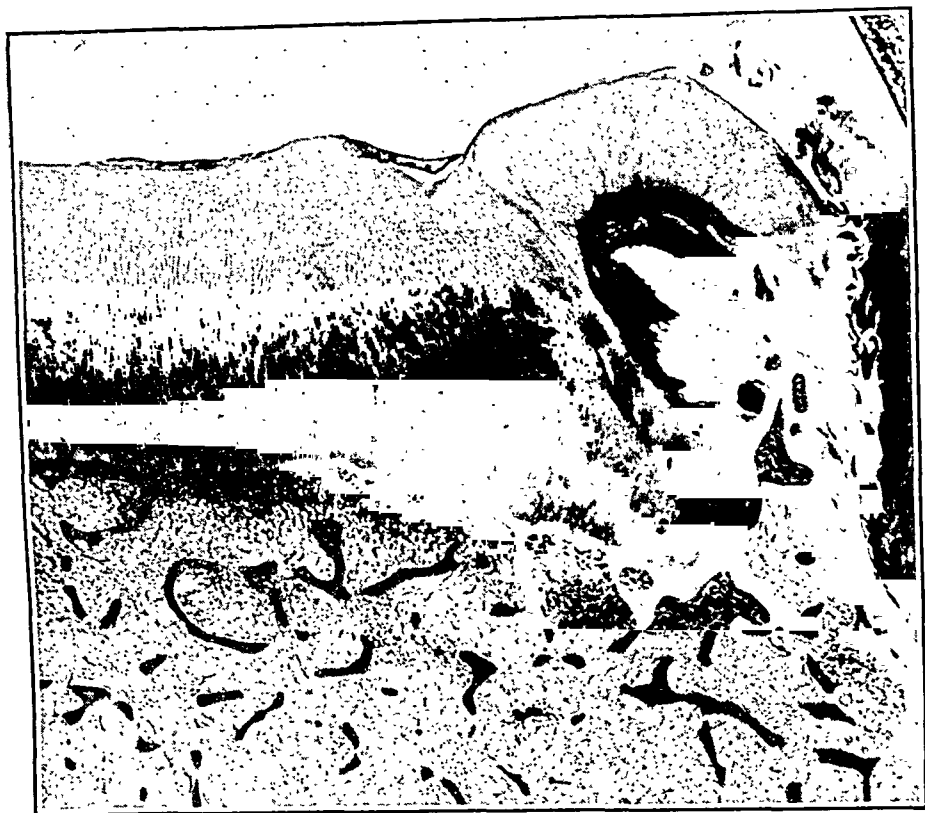


FIG. 9.—Lesions typical of advanced degenerative joint disease are illustrated in this reproduction of a transverse section of one margin of the patella.

Microscopic study of the proximal and distal interphalangeal joints of 1 toe revealed singularly interesting alterations in the hyaline cartilage (Figs. 11 and 12). The calcified stratum was increased in thickness. The lowermost hyaline layer showed an abnormal preponderance of matrix over cells, while in the adjacent zone the cell columns were more prominent and more transversely arranged than in the normal. The individual lacunar spaces contained an excessive number of cells. The layer of columnar chondrocytes was increased in size and there was evidence of active cellular proliferation. It seems important to point out that these changes were not associated with superficial erosion of cartilage, and the usual early histologic manifestations of degenerative joint disease were slight or absent (Fig. 13). However, bony excrescences and tufting were noted about the terminal phalanx.

The costochondral junctions were the site of severe and uncommon pathologic alterations (Figs. 14, 15 and 16). Instead of a nearly linear separation between bone and cartilage, there was a wide and diffuse area of transition which, in contrast to normal, showed considerable enlargement in all dimensions (Fig. 5). The center of the lesion was characterized by an irregular advance of vascular marrow into the chondral part of the rib. Where such



invasion had taken place, there was frequently evidence of active bone formation. Interspersed between the foci of ossification were pleomorphic islands of degenerating and proliferating cartilage. The more recently formed hyaline cartilage located in the peripheral part of the rib likewise showed active proliferation with voluminous cells. The perichondrium had apparently been replaced by a sheath of periosteum and bone, continuous with the osseous shaft of the rib.



FIG. 10.—Synovial tissue of the knee showing mild diffuse inflammatory cell infiltration of the superficial zone. The curious edematous and myxomatous change prevailing in many parts of the connective tissues is indicated in the lower half of the photograph ( $\times 75$ ).

**Discussion.** To interpret the various findings pertaining to the articular structures in this case, it seems advisable to consider first those lesions which appeared familiar from previous observations. The vertebral column showed gross, microscopic and radiologic alterations, the greater part of which were wholly consistent with degenerative joint disease of the spine and which we were able to match in

most details with material from elderly non-acromegalic subjects. There are, however, three qualifications to this similarity. First, the degree of hypertrophic bone changes at the margins of the intervertebral articulations, as evident in the roentgenogram of the excised



FIG. 11.—A photomicrograph ( $\times 8$ ) of the terminal phalanx and distal articulation of the second toe. Note the irregular bony overgrowth about the end of the phalanx. The articular surfaces show little evidence of degenerative joint disease.

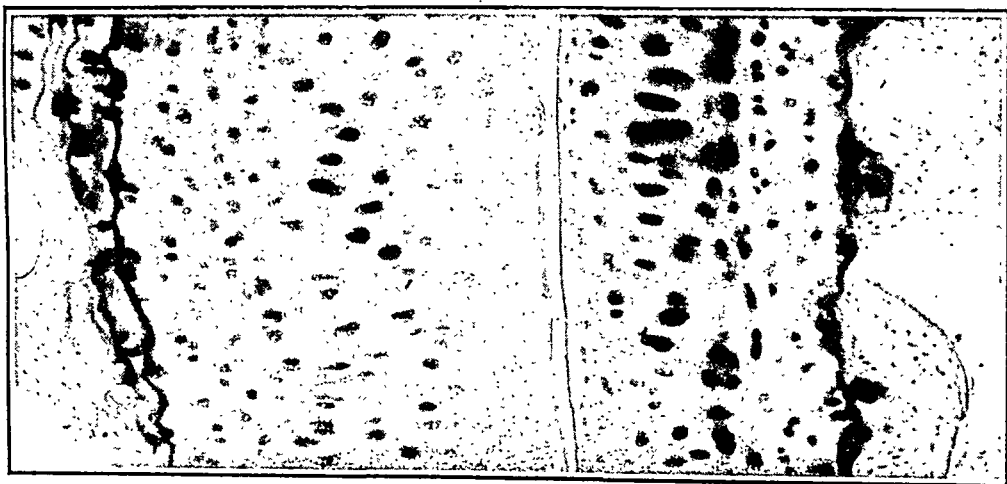


FIG. 12.—Opposing articular surfaces of the terminal phalangeal joint of the toe illustrated in Figure 11 are shown in this photomicrograph ( $\times 75$ ). The deepest third of cartilage shows fewer cell groups than normal. Their distribution, however, is not unusual. In the middle third the cartilage cells are exceedingly numerous and arranged in irregular columns and clusters. The superficial third of each articular surface is normal or shows only minimal degenerative changes.

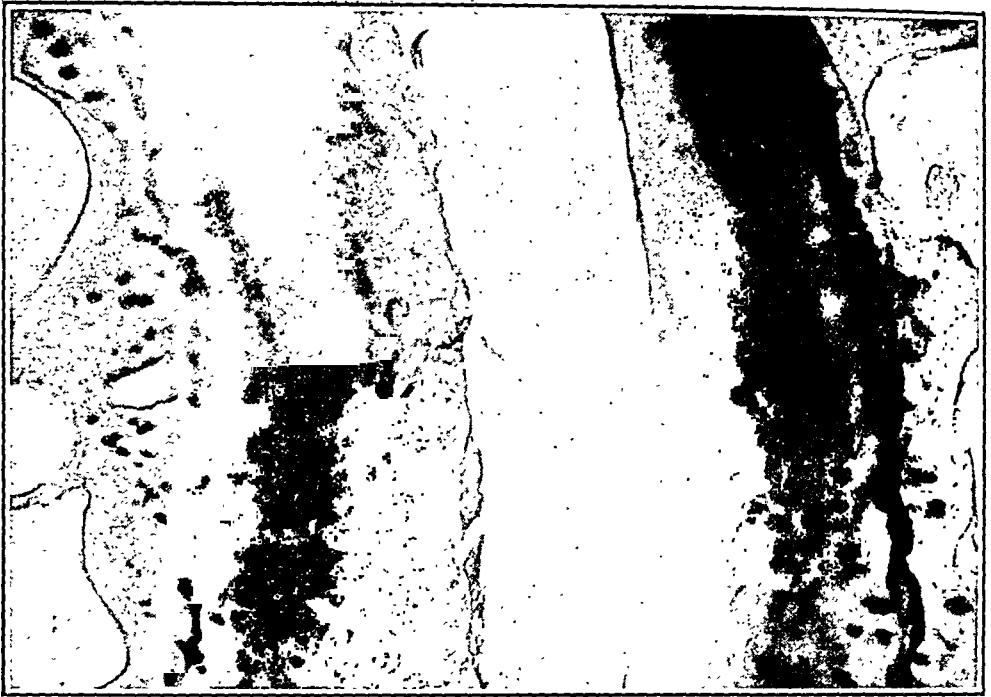


FIG. 13.—A photomicrograph ( $\times 75$ ) of a portion of a terminal phalangeal joint of a non-acromegalic elderly man showing the usual changes of degenerative joint disease. The superficial portions of each cartilaginous surface show alterations, whereas the deeper portions are normal. This photograph should be compared with Figures 11 and 12.



FIG. 14.—A portion of a section of an expanded rib cartilage (see Fig. 5) is reproduced in this photograph ( $\times 8$ ). Note the evidence of active cartilage cell proliferation and the irregular islands of ossification. The segment illustrated was several centimeters distal to the normal costochondral junction.



FIG. 15.—Active endochondral ossification is indicated, in this photomicrograph ( $\times 75$ ) of the cartilaginous portion of a rib, by the apparent bony replacement of the transversely placed cartilage cell columns. This reactivation of growth sequences has led to the formation of a bony sleeve around the rib cartilage. To the right of the photograph is an island of fully developed cancellous bone that has replaced the original cartilaginous tissue.



FIG. 16.—A portion of an enlarged rib cartilage is shown in this photomicrograph ( $\times 75$ ). The clustering and immaturity of the cartilage cells is indicative of pronounced proliferative activity. Irregular areas of ossification are apparent.

spine (Fig. 4), is unusually marked. Second, in contrast to the usual relationship, the segments T11 and 12 appeared slightly larger in transverse diameter than the lumbar vertebrae L1 and 2, disregarding, of course, the exostoses. This discrepancy is visible also in the Roent-

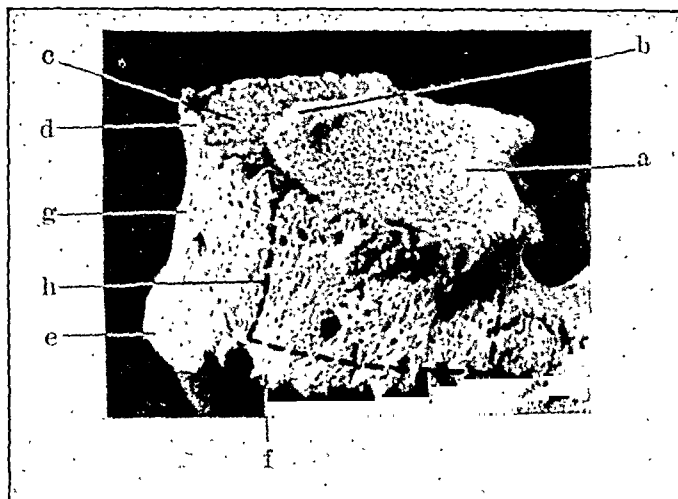


FIG. 17.—Relation of the newly formed bone to the original vertebral body. The lines drawn in the figure show that the perforated surface (*a*) and the edge (*b*) of the old vertebral body are located inside the newly formed bone. The latter has a dented edge (*f*) but shows no exostoses either at (*d*) or (*e*). Like a normal vertebra, it is slightly concave in the front. The old periosteal contour is sunken and runs parallel to the new one. (From J. Erdheim, *Über Wirbelsäulenveränderungen bei Akromegalie*, Virchows Arch. f. path. Anat., 281, 197, 1931.)

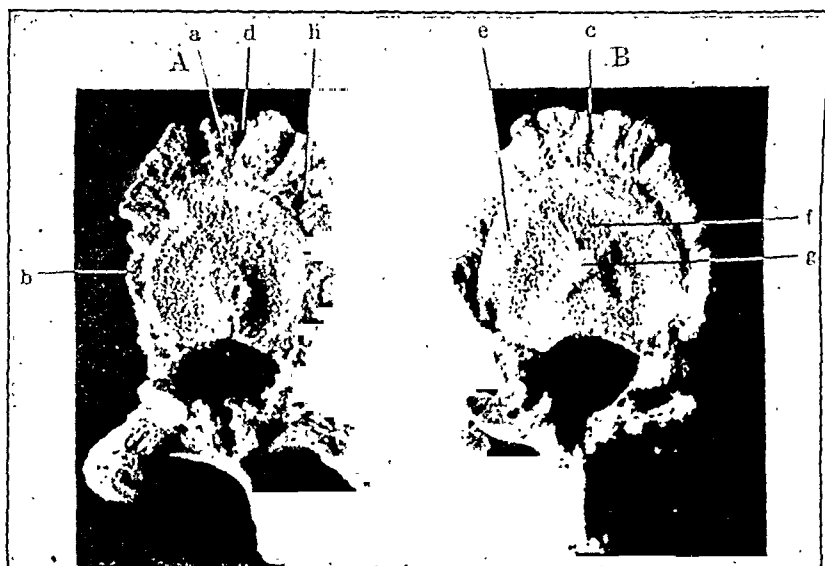


FIG. 18.—Here one notes the diaphyseal origin of the newly added bone on the lower surface of the 3rd lumbar vertebra. The edge of the old vertebral body (*a*) casts the shadow (*c*) on the newly formed bone (*b*), which does not originate from the marginal edge (*d*) but from the periosteal surface of the diaphysis. (From J. Erdheim, *Über Wirbelsäulenveränderungen bei Akromegalie*, Virchows Arch. f. path. Anat., 281, 197, 1931.)

gen ray photograph (Fig. 4). Lastly, there was complete and fairly extensive bony union between the dorsal vertebræ, D6 and 7, associated with exceedingly severe degeneration of the intervening disk. Judging from the microscopic appearance, this lesion appeared to be of several months' duration and could not be attributed, either clinically or histo-

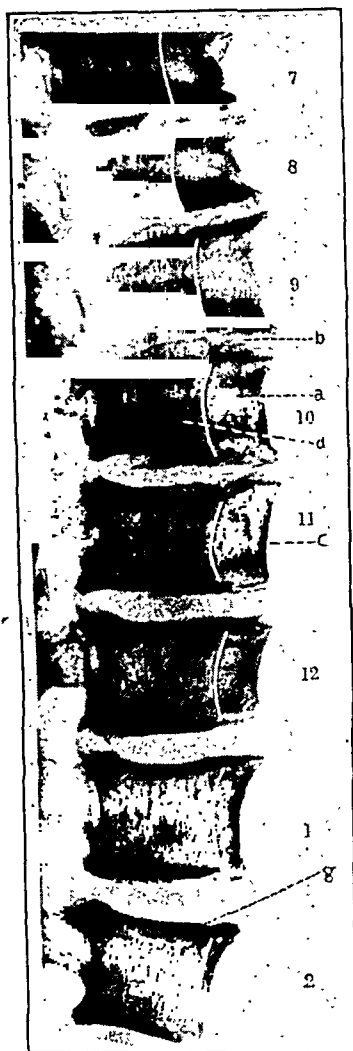


FIG. 19.—Roentgenogram of one-half of the vertebral column, including the 7th dorsal to the 2nd lumbar vertebræ. The white line separates the old vertebral bodies and the newly laid down bone. Contrary to the general rule, the bodies of the lower vertebræ become smaller. However, less newly formed bone is found in the lower vertebræ, thus indicating, as is normally the case, that the original vertebral bodies are larger in the lower portion of the vertebral column. (From J. Erdheim, *Über Wirbelsäulenveränderungen bei Akromegalie*, Virchows Arch. f. path. Anat., 281, 197, 1931.)

logically, to an infectious process. Although on careful questioning the patient had denied any pertinent injuries, the lesion may, of course, have been the result of trauma, either alone or as an adjunct in causing a pathologic fracture. Whether the deviations from the common picture of degenerative disease of the spine, noted in this patient,

represent incidental and disconnected findings or are related to the specific articular lesion of acromegaly cannot be decided on the basis of the material in our hands. The latter interpretation would be consistent with the conspicuous evidence of generalized active endochondral ossification in the vertebral bodies. Certainly the vertebral alterations did not approach in appearance the fully developed acromegalic spine lesions which Erdheim found in 1 of the 2 cases he reported.<sup>3</sup>

To facilitate a comparison with the pathologic findings described in this case, Erdheim's description may be summarized briefly. In essence, the acromegalic spine is distinguished by additional growth of the vertebral bodies and of the intervertebral disks. The bony increment develops from the periosteum and by endochondral ossification of proliferating cartilage. It is more evident on the anterior and lateral aspects of the vertebral column than posteriorly (Figs. 17 and 18). The newly formed bone is demarcated, very clearly in the Roentgen ray, and to a lesser extent in microscopic section, by the irregular arrangement and deficient calcification of the trabeculae (Fig. 19). The new cortex is pathologically wide and the increased transverse diameter of the vertebral body may give the mistaken impression of reduced height. The new disk segment arises from the perichondrium and is well differentiated into the various normal components, including the calcified layer and the hyaline plate. Certain criteria may be used to distinguish between acromegalic and purely degenerative disease of the spine. In the latter, marginal exostoses develop in response to degeneration of the disks and therefore vary in location and degree. The bony new-growths occurring in the former are independent of and may be present without any degeneration of the intervertebral disks. They are more uniformly distributed throughout the vertebral column. It need not be emphasized that both types of lesions may be and indeed have been found in the same patient. Conversely, not every acromegalic individual will show the specific articular changes in all sites.

The lesions observed by us in most of the peripheral joint surfaces examined did not reveal any distinctive features. To be sure, the degree of hypertrophic bone reaction again was striking, but the pathologic process conformed in essentials to the familiar pattern of marked degenerative joint disease. The exception to this was found, however, in the changes in one toe joint, which were inconsistent with the common type of senescent arthropathy but compatible with the changes described by Erdheim.<sup>2</sup> Whereas in the former, the earliest histologic stigmata are swelling and fibrillation of the matrix of the superficial hyaline covering, leading to its erosion and the well-known subsequent alterations in the joint margins, subchondral bone and synovialis,<sup>1</sup> the acromegalic change was found by Erdheim to begin with hyperplasia and hypertrophy of the columnar zone of chondrocytes associated with an increase in matrix.<sup>2</sup> The deepest, calcified layer cannot, in the adult joint, participate in this juvenile type of reaction, although it shares in the relatively slower process of endochondral ossification advancing from the subchondral marrow. This

disparity in reaction, as well as the rapid disorganization of the columnar cartilaginous zone which is primarily responsible for elastic action, renders the articular cartilage vulnerable to functional stresses, subsequently produces clefting and fibrillation and engenders, at last, a pathologic picture identical with that of degenerative joint disease. As Erdheim pointed out, the difference between the two entities is clearly discernible only in their incipient stages. To demonstrate the distinguishing features, we have included the microphotograph of a finger joint from a patient with senescent degenerative joint disease (Heberden's node) (Fig. 13 for comparison with Figs. 11 and 12).

Microscopic lesions, such as those observed in the costochondral cartilages, we could not recall having encountered heretofore. The alterations consist of marked and irregular hyperplasia and hypertrophy of chondrocytes and increase in matrix in the middle cortical portions of the cartilaginous rib. Coupled with these phenomena is a progressive endochondral ossification at the cartilage bone border. The former are responsible for the prominent beading shown in the photograph of the patient and in the Roentgen ray film of the rib specimen (acromegalic rosary) (Fig. 5). The latter results in advance of the vascular bone marrow into the central avital part of the chondral cartilages and in increased periosteal bone formation at the periphery, so that for a short distance, two concentric layers of trabecular bone may be seen to envelop the former cartilaginous cortex (Fig. 14). Thus, nodal as well as circumferential growth has occurred at the cartilage bone border and has led to the abnormal expansion of the thorax, long known as one of the striking characteristics of acromegaly. A comparison between our sections and those shown by Erdheim reveals close similarity in every essential detail.<sup>2</sup>

**Conclusion.** The gross and microscopic pathologic findings in representative joints of an acromegalic patient have been reported. It was found that in many respects, particularly where there were advanced alterations, the histologic picture closely resembled that of severe degenerative joint disease. In some features and in a few individual sites, however, the changes appeared to be of a wholly different nature and could not be regarded as reactions to primary degeneration of cartilage. These particular phenomena, principally new-growths of cartilage and bone, appeared to indicate reactivation of cartilage growth and enhanced endochondral ossification, unphysiologic at the age of this patient and perhaps the result of a specific hormonal stimulus.

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# PROGRESS OF MEDICAL SCIENCE

## RADIOLOGY

UNDER THE CHARGE OF

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### NOTES ON A VARIETY OF ROENTGENOLOGIC PROBLEMS

By HARRY M. WEBER, M.D.

**Choledocholithiasis.** It has been said<sup>3</sup> that a patient with gall stones has a 13 to 20% chance of having 1 or more stones in the common bile duct. This estimate of the incidence of choledocholithiasis was based on a study of published figures from several large clinics, so it may be regarded as a reasonably accurate one. An unqualified roentgenologic diagnosis of stone in the common bile duct is but rarely made. Since the common bile duct is hardly ever depicted on cholecystograms, the stones it might contain must be of the so-called opaque variety, that is, they must contain an adequate amount of calcium if they are to be depicted on cholecystograms; such stones would be demonstrable roentgenographically without the administration of a cholecystographic medium. Roentgenographic demonstration of so-called non-opaque stones in the common bile duct would require a most fortuitous combination of circumstances; to accomplish it otherwise the common bile duct must be made accessible, by means of choledochostomy, for direct injection with a fluid contrast medium. This procedure is known as cholangiography.

Sahler and Hampton<sup>2</sup> have reported a series of 12 cases in which a preoperative diagnosis of choledocholithiasis was verified at operation. In all instances the stones contained enough calcium to make them demonstrable roentgenographically without the use of a cholecystographic medium. The authors noted that it is not generally appreciated that stones in the common bile duct can be shown in this way presumably because (1) the incidence of choledocholithiasis is relatively low, and (2) when present it is difficult to determine the position of the stones with accuracy. To reveal the stones, the roentgenograms must be of best quality. By means of antero-posterior and lateral projections of a normal cholangiogram, Sahler and Hampton showed that the common bile duct is projected below the lower right ribs, across the upper medial pole of the right kidney, so that its lower end overlies the renal pelvis, and that it occupies the center of the body in the antero-posterior plane. The gall bladder occupies a much more anterior position in the body. When choledocholithiasis is suspected, Sahler and Hampton recommended that stereoscopic or both postero-anterior and lateral roentgenograms be made.

In the postero-anterior projection shadows of stones in the common duct will be less distinct and more distorted than those of stones in the gall bladder because the latter concretions will be nearer the film. The distinction between renal calculus and stone in the common bile duct is made with the lateral view. In this projection, the stone in the common bile duct lies anterior to the spine, whereas urinary calculi are projected over the spine unless the kidney happens to be dystopic. A stone in the ampulla of Vater might lie far enough posteriorly to simulate a renal stone. In obscure cases, a urographic procedure was required to distinguish between renal stones and stone in the common bile duct. If, in an antero-posterior projection, a stone is shown to be in the immediate vicinity of the duodenum or in the duodenal loop, it will usually prove to be in the common bile duct, since it will then be below the junction of the common bile duct and cystic duct. Sahler and Hampton used this maneuver to distinguish between stone in the cystic duct and stone in the common bile duct and called attention to the development of hydrops of the gall bladder when the cystic duct is occluded by calculus. They encountered no remarkable difficulty in distinguishing choledocholithiasis from other calcified masses in the right upper abdomen, such as calcified costal cartilages, echinococcus cysts and calcified abdominal vessels. Choledocholithiasis should be suspected in all cases in which calcification is seen in the region of the gall bladder and common bile duct, in cases in which milk-of-calcium bile is demonstrated, and in cases in which the patients are jaundiced. It seems apparent that with a more extended use of these simple maneuvers the roentgenologic examination can be made to contribute somewhat more than it has in the past to the diagnosis of choledocholithiasis.

**Adenoma of the Bronchus.** This benign sounding name is applied to a neoplasm which in a strict pathologic sense, at least, is a malignant one. It grows slowly, but it actually invades the bronchial wall; its cells tend to be poorly differentiated and to be arranged in a disorderly fashion. Metastasis occurs, but rarely, and then only after a period of several years. Lowry and Rigler<sup>1</sup> recognized this somewhat anomalous situation, and in a very illuminating and convincing paper they pointed out that bronchial adenoma does not act like the more familiar, because so much more frequently encountered, type of bronchogenic malignant lesion, but like a benign lesion. They emphasized that the disease which adenoma of the bronchus produces has a fairly characteristic clinical pattern of its own, quite different from that of the ordinary run of frankly malignant tumors of the bronchi. They showed that by recognizing this pattern and by exacting the full yield of modern roentgenologic and bronchoscopic techniques including biopsy, the two diseases can quite readily be distinguished from each other, and in relatively early stages. They argued that this differentiation is important, for the adenoma has by far the more favorable prognosis to begin with, and because it is so much less lethal it is probably safe in most instances for the physician to gamble with the less radical therapeutic procedures, and so the ultimate prognosis is still more favorably influenced.

Some of the points Lowry and Rigler made might well bear repetition and reconsideration in these pages.

About 6% of primary tumors of the bronchus are adenomas. This may seem to be a low incidence, but Churchill is quoted to the effect that about a fourth of all resectable tumors of the bronchi belong in this group; therefore, among the curable bronchial neoplasms, adenoma is relatively

common. Almost 80 % of patients with adenoma have symptoms before the age of 40, many much earlier than that; 90 % of the victims of carcinoma are over 40. Sixty % of bronchial adenomas occur in women; 90 % of bronchial carcinomas occur in men. These striking contrasts suggested strongly to Lowry and Rigler that the 2 tumors are fundamentally different and not merely grades or stages of the same kind of neoplasm.

It is generally held that bronchial adenomas originate in the epithelium of the bronchial mucous glands, for they are found practically only in bronchi 10 mm. or more in diameter, where the mucous ducts also occur. This theory of their origin also helps to explain the occurrence, in many of the cases, of extension of the tumor through the bronchial wall beyond the cartilaginous rings, a layer also penetrated by the mucous ducts. Bronchial adenomas are true tumors; they are the cause, not the result, of the inflammatory processes so often seen in association with them. Grossly, they are smooth, round or oval, pink, sessile or pedunculated masses, sometimes extending through the bronchial wall to form extra-bronchial portions larger than the intrabronchial. Small, and cuboidal or polygonal in shape, the neoplastic cells tend to be uniform in size and staining properties and to look undifferentiated; they grow in irregular masses and cords, sometimes form acini; mitotic figures are few in number. Growth is slow, but the tumor gradually occludes the bronchus in which it arises, and in this process repeated infections occur aborad to the occlusion. Sooner or later, part of the affected lung is destroyed by recurring infection. Bronchiectasis is almost inevitable, and the more acute infectious processes such as suppurative pneumonia, abscess and empyema may eventually prove fatal.

The history and physical signs depend entirely on the degree of bronchial occlusion which develops and upon the type and extent of the secondary changes which have been produced in the affected lung. Prominent in the histories of the cases are bouts of pulmonary infection, some of which are severe, slow to resolve, and featured by cough, purulent sputum, fever, pleuritis—all occurring repeatedly and obviously arising from the same part of the lung. Between such attacks the patient may be in good health although the cough often persists. The steady downhill course of the disease produced by the frankly malignant bronchial neoplasms is in sharp contrast to the characteristic periods of remission. Hemoptysis occurs at some time or other in two-thirds of the cases. This is often profuse; it tends to start and end abruptly, and seems to accompany the menses in women more often than does hemoptysis from other causes. The cough may be productive or not. Wheezing, cyanosis and dyspnea are observed in advanced cases. Early in the course of the disease there may be no abnormal physical signs; late in the course, the signs are those of total atelectasis. In some of the cases there is clinical evidence of obstructive emphysema; in practically all of them bronchiectasis develops within a year or two after the onset of symptoms.

Roentgenologic examinations have a rôle of first importance in the diagnosis of bronchial adenoma. Cases have been reported in which no abnormal roentgenologic findings could be elicited, but Lowry and Rigler had no such experience and they expressed the opinion that the situation must be exceedingly rare. Roentgenologic diagnostic maneuvers include the standard antero-posterior and lateral projections of the thorax, bronchography, and body-section roentgenography. Atelectasis, total or partial, commonly accompanied by the "drowned lung" phenomenon, is a frequent finding; if intermittent and recurrent, this finding is especially character-

istic. In other instances the pneumonitis, likewise remittent and recurrent, is the prominent roentgenologic finding, and the pulmonary changes as depicted on the roentgenograms strongly suggest those of an atypical pneumonia. Evidence of bronchiectasis localized to a single lobe should always make the diagnostician think of bronchial adenoma. A mediastinal mass with associated evidence of bronchial obstruction is to be considered as a possible extrabronchial extension of an adenoma of the bronchus. With bronchography it is possible to demonstrate the bronchiectasis and the site of the bronchial obstruction with great accuracy. A "cap-shaped" deformity of the bronchial outline, due to a layering of the opaque oil over the round, smooth, intrabronchial mass, is characteristic. Carcinoma of the bronchus produces a more diffuse elongated "rat-tail" type of deformity of the bronchial lumen. With body-section roentgenography Lowry and Rigler succeeded in demonstrating the intrabronchial mass of the adenoma directly, the air in the bronchus serving as a contrast medium. It was not possible, however, to do this in all instances. They also found repeated roentgenologic examinations of inestimable value in pursuing their studies of their cases.

The final diagnosis of bronchial adenoma is made by bronchoscopic examination at which the gross features of the lesion are characteristic. Biopsy or other instrumentation may cause free bleeding which may be profuse enough to occlude all or a portion of the bronchial tree of the affected side. Lowry and Rigler prefer to let the clot liquefy and be removed by natural processes. Such removal ordinarily takes place within a few days. They warned that attempts at bronchoscopic removal of the clot are often followed by more hemorrhage.

Pathologic diagnosis by means of small sections of tissue removed by bronchoscopic biopsy are reliable, of course, only if actual and representative neoplastic substance is delivered to the pathologist. This is not always possible. In any event, Lowry and Rigler recommended that the diagnosis of adenoma of the bronchus be made to rest on the composite results of clinical, roentgenologic and bronchoscopic examination; if all these are in accord and indicate adenoma, a conflicting pathologic report should not be accepted as the final diagnostic word.

Treatment has been along 3 different lines: Bronchoscopic removal seems to have the most to offer to patients in whom the adenoma is discovered early before it has produced much damage to the lung. This method of treatment is favored, too, if the lesion involves the main bronchus so that pneumonectomy would be required for radical removal, in patients who refuse pulmonary resection, and in those whose tumor is so situated that resection is impossible. Patients who are advised to accept lobectomy or pneumonectomy are also advised to undergo preliminary local removal to provide for optimal preoperative drainage of suppurative areas in the lung so as to minimize the surgical risk. Experience with irradiation is too limited to make a satisfactory estimate of its efficacy. Physicians who have used it most find that bronchial adenomas are somewhat sensitive to irradiation therapy, and further investigation with carefully controlled dosage is in order. It is clear that pulmonary resection with total removal will give the most desirable end-result in the treatment of a neoplasm having the maleficent possibilities this one has, but the risk that has to be assumed is a disturbing feature. Lowry and Rigler hold that each case must be assessed individually with respect to the size, site and extension of the tumor, and the amount of pulmonary damage the tumor has produced. On this basis, they form a rough idea of the patient's

prognosis if the tumor is not removed radically, and against this prognosis they weigh the risk of the procedure considered necessary to extirpate it. A few patients are selected to undergo local removal of the tumor. Since the surgical risk of lobectomy is now so low, they advised this procedure if the adenoma is so situated that it can be removed by lobectomy or combined resection of the lower and middle lobes. Pneumonectomy carries with it a considerably higher surgical risk, so that when this procedure is required Lowry and Rigler prefer to advise bronchoscopic removal and observe the patient for a year or two. If there is no recurrence, and if the symptoms disappear, the patient is merely kept under observation. With rapid recurrence of the tumor, or with persistence of troublesome symptoms, or with evidence of the presence of a large extra-bronchial extension of the growth, especially if it is increasing in size, pneumonectomy is reluctantly recommended as the less dangerous of two hazardous alternatives.

With detailed and well-illustrated reports of 7 cases the clinical, roentgenologic and therapeutic features of this most interesting pulmonary disease were exemplified.

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### THERAPEUTICS

UNDER THE CHARGE OF

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The Editors regret that through unavoidable circumstances it has become impossible to have a progress article in this department for this number.

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### PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 20, 1945

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**Studies on the Prolonged Maintenance of Adult Dogs on a Purified Diet.**  
A. O. SEELER and R. H. SILBER (Merck Inst. for Ther. Research). Six adult female dogs were placed on a basal diet which according to present knowledge had no significant amounts of vitamin B complex factors. In addition to the fat-soluble vitamins this diet was supplemented with adequate amounts of thiamine, riboflavin, pyridoxine and nicotinic acid. Two of the dogs were also given pantothenic acid. One of the dogs on the pantothenic acid-deficient diet began to lose weight after 7 months and died in the 9th month; 2 remained well until the 15th month when they

too began to lose weight. Their condition 17 months after the beginning of the experiment was critical and they were given pantothenic acid. Their response to the vitamin was prompt and within a month the dogs appeared normal again. One of the 4 dogs on the pantothenic acid-deficient diet showed no gross evidence of disease after  $4\frac{1}{2}$  years on the diet. Three of the 6 dogs were still in apparent good health after  $4\frac{1}{2}$  years on a diet and supplement containing no significant amounts of biotin, inositol or folic acid complex. While choline was not given *per se*, the diet contained 30% casein and consequently had a relatively large amount of methionine. Hematologic studies and blood chemical determinations failed to reveal any abnormalities in these animals. Kidney function tests were negative. Bromsulfalein retention was, however, somewhat greater than at the beginning of the experiment suggesting moderate liver damage.

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**Experimental Studies on the Excretion of Neutral Red by the Stomach.** R. KOLM, S. KOMAROV, and H. SHAY (Med. Research Lab., Samuel S. Fels Fund). The effect of neutral red on gastric secretion and the mechanism of its excretion by the stomach were studied in acute experiments on 17 dogs and 6 cats. Neutral red was found to act as a mild gastric secretagogue when injected intravenously in doses from 7.5 to 20 mg. per kg. body weight. It produced uniformly a small increase in the rate of gastric secretion as well as an increase in acidity or a diminution of alkalinity. In most experiments there was also an increase in pepsin concentration. These effects especially on the peptic cells were prevented largely by preliminary atropinization and to a lesser degree by double cervical vagotomy. In contrast to the action of atropine upon the neutral red effect upon the peptic cells, repeated large doses of this drug failed to abolish completely the stimulating action on the parietal cells.

Neutral red was not excreted by the pyloric mucosa. Evidence is presented that neutral red is not excreted by either the mucous, mucoid cells or the peptic cells. In atropinized animals, neutral red was absorbed and stored for many hours as a yellow pigment by the parietal cells when these cells were not secreting actively and at a time when neutral red excretion in the urine had already reached very low levels. Subsequent administration of histamine (3 to 6 hours after the injection of neutral red) caused the elimination of large quantities of neutral red with the gastric juice. After histamine, the increase in concentration of neutral red paralleled the acidity and concentration of pepsin. As the histamine action continues, there is a diminution in the concentration of neutral red excreted. This decrease is paralleled by a decrease in the concentration of pepsin even if the acidity and rate of gastric secretion continues to rise. Parallelism between the concentration curves of neutral red and pepsin under these conditions is regarded as an expression of the "washing out" process described by Babkin for the action of histamine upon peptic secretion.

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**The Mechanism of the Virucidal Action of Ascorbic Acid.** MORTON KLEIN (Dept. of Bacteriology, Univ. of Penna.). It has been reported that ascorbic acid is virucidal for the viruses of rabies, vaccinia, poliomyelitis, and influenza virus. Chemical studies of the oxidation of ascorbic acid have revealed that during the Cu catalyzed oxidation of ascorbic acid  $H_2O_2$  is formed. It would seem reasonable to assume that the viru-

cidal action of ascorbic acid may be due to the  $H_2O_2$  formed during the oxidation of the compound.

The PR8 strain of influenza A virus, grown in the allantoic sac of the developing chick embryo, was the test virus and intranasal mouse inoculation was used for indicating viral activity. It was found that 0.05 M ascorbic acid diluted in phosphate buffer, pH 7, inactivated 10 MLD of influenza A virus. Catalase, which is known to specifically inactivate  $H_2O_2$ , was found to neutralize completely the action of ascorbic acid.  $H_2O_2$  (0.1%), which approximated the concentration of  $H_2O_2$  produced under the conditions of our experiment by 0.05 M ascorbic acid, also inactivated 10 MLD of influenza virus and this inactivation was completely neutralized by catalase.

It is concluded that the virucidal action of ascorbic acid may be explained as being due to the production of  $H_2O_2$  formed during the Cu catalyzed oxidation of ascorbic acid.

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**Chemical Structures of Co-factors for Bacterial Viruses.** T. F. ANDERSON (E. R. Johnson Research Foundation, Univ. of Penna.). Of a group of 7 viruses\* (bacteriophages) active on the strain B of *E. coli*, 2, T4 and T6, are very slowly adsorbed on the host in synthetic ammonium lactate medium. Adsorption of T4 and T6 has been found† to be rapid only in the presence of certain co-factors of which *l*-tryptophane is the most active. Out of 47 other compounds tested with T4, only *dl*-phenylalanine, *dl*-tryosine, *dl*-diiodotryosine, *dl*-Bz-3-methyltryptophane and *dl*-Pr-2-methyltryptophane are active. The inactivity of members of a series of tryptophane analogues and derivatives indicates that for co-factor activity a tryptophane analogue must (1) have an intact  $\alpha$ -amino group (indole-3-propionic acid and amino-N-methyltryptophane are inactive); (2) have a free carboxyl group (tryptamine and 3-(3-indolyl)-2-amino-propanol (1) are inactive); and (3) have the *l*-configuration (*d*-tryptophane is inactive). The results suggest that in this case at least the process of adsorption involves something more than the simple fitting of structural parts of virus and host; a chemical reaction involving the co-factor may well have to follow the chance encounters between virus and host for the virus to be adsorbed and initiate its activity on the host.

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**Drying Penicillin.** EARL W. FLOSDORF and STUART MUDD (Dept. of Bacteriology, Univ. of Penna. and F. J. Stokes Machine Co., Phila.). Drying penicillin and drying plasma by sublimation in most respects are similar. The primary differences are (1) penicillin must be maintained at a lower temperature and (2) penicillin is dried in small volume per container.

The actual temperature of drying varies with the degree of purification and is usually on the order of  $-25^\circ$  to  $-30^\circ$  C. and lower. The reason for this low temperature is primarily not lability, but is because at higher temperature partial softening and consequent frothing under vacuum occurs.

Drying in small bottles causes greater hazard of thawing during the loading and evacuation of the drying chambers. For this reason, the

\* Demerec, M., and Fano, U.: *Genetics*, 30, 119, 1945.

† Anderson, T. F.: *J. Cell. and Comp. Physiol.*, 25, 17, 1945.

chambers are arranged for chilling to freeze the penicillin after loading but before evacuation.

Penicillin may also be dried in bulk and transferred subsequently to ampoules. This method has not met with favor because it is difficult to make bacteriologic sampling representative and there is less certainty of sterility.

Penicillin may also be dried as a liquid at about room temperature in a few minutes by means of dielectric heating at radio frequencies. Because of rapidity of drying there is no loss in potency even at the higher temperature. In order to prevent frothing of the material from ampoules, the bottles are rotated at high speed according to a method developed by Radio Corporation of America. The centrifugal action holds the penicillin solution next to the walls of the ampoules until drying is completed.

The required degree of final moisture is controversial because insufficient data have been accumulated until now. However, a moisture content of about 0.5% is best for greatest certainty of preservation, this allowing some margin for increase during distribution to the market.



# BOOK REVIEWS AND NOTICES

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MEDICO-LEGAL BLOOD GROUP DETERMINATION. By DAVID HARLEY, M.D., B.Sc., F.I.C. From the Laboratories of the Inoculation Department, St. Mary's Hosp., London, England. Pp. 119; 13 figs.; 23 tables. Second impression. New York: Grune & Stratton, 1944. Price, \$3.50.

THIS little book is a summary, by a British author, of the human blood grouping tests. Emphasis is placed on their application to the problems of disputed parentage and blood and secretion stain identification. The book is divided into 3 main sections. The first part considers the A-B-O and M-N blood types and their heredity. In the second part apparatus and techniques are discussed. The last section is devoted to the history of the application of these tests to medico-legal problems, most examples being drawn from the English courts. The author pleads for legislation enabling the English courts to order the performance of these tests. Let us hope his plea will be heard in the United States, where only a few of the "more enlightened" states (New York, Wisconsin, Ohio, Maine, New Jersey, South Dakota, and Maryland) have adopted adequate legislation.

There is no mention of Rh blood typing. It is true that as yet Rh tests have had almost no application in the courts. However, as they will undoubtedly be used more and more as a supplement or as a check of the other major grouping tests, some mention should have been made. As a summary, this volume makes easy and rapid reading, but it is of course not to be considered as a substitute for the standard reference works. W. S.

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THE EXPERIMENTS OF NATURE AND OTHER ESSAYS. Porter Lectures, Series XII. By IRVINE MCQUARRIE, Ph.D., M.D., Department of Pediatrics, Univ. of Minnesota. Delivered at the Univ. of Kansas School of Medicine. Lawrence, Kan.: Univ. of Kansas, 1944. Price, \$1.00.

THE first of these 3 essay-lectures, titled with a happy phrase from Osler, declares that the intelligent study of sick patients will sometimes uncover new physiologic principles of a sort which might never enter the purview of investigators working with normal experimental animals. Clinicians therefore should study completely all curious phenomena observed at the bedside, utilizing the rich library and laboratory facilities this country's hospitals so bountifully provide. This thesis is more than adequately proved by descriptions of a half-dozen unusual metabolic disturbances, with illuminating expositions of the contribution to medical progress each one exemplifies. The second essay presents a series of brilliant case studies illustrative of the variety of disorders resulting from dysfunctions of the adrenal glands in childhood. The final essay recounts interesting experiences with parasitic, nutritional, and other oriental diseases encountered by the author while serving as visiting professor of pediatrics at Peiping Union Medical College in besieged China during 1939-1940. This small scholarly volume should be read by all pediatricians and internists who desire to keep abreast of the advances in our understanding of unfamiliar and esoteric diseases. I. W.

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TRICHINOSIS. By SYLVESTER E. GOULD, M.D., D.Sc., Pathologist and Director of Laboratories, Eloise Hosp., Eloise, Mich.; Assistant Professor of Pathology, Wayne Univ. Coll. of Med., Detroit. Pp. 356. Springfield: Thomas, 1945. Price, \$5.00.

*Trichinella spiralis*, like lice and itch mites, is dependent for its maintenance in man and in swine upon certain rather firmly established patterns of human

behavior. And mankind being what it is, the parasite apparently has little need for concern over its future. For so long as feeding uncooked garbage to swine is profitable, and pork from this source brings a good price, trichinosis will certainly occur. Over the past century, since the parasite was first recognized, it has stimulated a considerable number of publications, for trichinosis should interest the clinician, the pathologist, the geologist, the epidemiologist, the swine grower, the veterinarian and the meat packer, and on occasion has been the subject of international controversy. Dr. Gould has prepared an excellent review of this extensive material. The subject matter is presented under the following chapter headings: I. Historical; II. Life Cycle; III. Morphology; IV. Epidemiology; V. Trichinosis in Animals; VI. Pathology; VII. Immunology; VIII. Laboratory Diagnostic Methods; IX. Symptomatology; X. Diagnosis; XI. Treatment; XII. Prognosis; XIII. Control Measures. The book is well written, excellently pointed and illustrated. It can be recommended without reservation. Both author and publisher are to be congratulated. H. R.

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PATIENTS HAVE FAMILIES. By HENRY B. RICHARDSON, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Cornell Univ. Med. Coll.; Attending Physician, New York Hosp.; Visiting Physician, Bellevue Hosp. Pp. 408. New York: The Commonwealth Fund, 1945.

DURING the recent decades American medicine has been fundamentally changed by the rapid expansion of medical knowledge and technique, great improvement of medical education and extensive development of hospitals, laboratories, and facilities for research. These changes have such obvious advantages for the medical profession in the study and treatment of disease that little consideration has been given to the disadvantages they might bring to the patient. It is true that the older generation sometimes bemoaned the disappearance from urban life of the family physician, and it became fashionable for doctors to talk about the importance of treating the patient rather than his organs. However, in the present era of "hospital medicine" not much was done to bring the patient as a person out of his relative obscurity. Recently, however, interest has grown in the social aspects of illness and medical educators and some practitioners have begun to realize that the mind, the emotions, and the environment of patients deserve greater consideration and study, if medical practice is to render the type of service that the people of this country should receive.

The book "Patients Have Families" is representative of this awakening. It is based upon an intensive coöperative study of the families of patients, directed by a physician, the author, with the participation of a psychiatrist, a social anthropologist, and the directors of a medical social service, a family social service, and an educational nursing service. The author has drawn also from his own experience as a physician.

In the first part, families are described and discussed as the unit of illness. An interesting concept of "family equilibrium" is presented which sets forth the various social and emotional forces within the family that determine its characteristics and its relations to illness.

The second part is entitled "The Family as the Unit of Treatment." The life of a true family physician is described, followed by a discussion of the responsibility of the physician to the family and the value of coöperation of psychiatrist and physician. The family is then considered from the point of view of the family case worker, the medical social worker, and the public health nurse.

In the third part, entitled "Present and Future," the family in war time is discussed, and is then considered in its relation to hospital practice and to medical teaching with a final discussion of the family unit as a subject of research. In a long appendix the method of study is described and the various professional techniques that were used are exemplified.

The book contains much that is valuable and interesting and is perhaps a

unique contribution to medicine. It suffers, however, from poor organization and fails to give concrete ideas in regard to some of the topics with which it deals. It is at times tedious and involved and is not easy reading, although it deals with material of human interest that has been thoroughly and competently studied and is brightened here and there by the author's sense of humor. A good many examples of faulty hospital practice are discernible in the accounts of the treatment of patients composing the families that are discussed, and no doubt these faults were a factor in stimulating the intensive study that was carried on for 2 years.

The title of the book is evidence that the author believes that the medical profession needs to be reminded of this fact. He emphasizes the importance of giving consideration to the patient not only as a total individual, but also as to his social setting, and shows how the interplay of forces within the family which constitute family equilibrium may be poorly balanced and thus become a fundamental factor in the cause and maintenance of illness. Unless this factor is included in the consideration of illness, medical care, especially in hospital practice, may be frustrated. G. R.

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POET PHYSICIANS. An Anthology of Medical Poetry Written by Physicians. Compiled by MARY LOU McDONOUGH. Pp. 210. Springfield, Ill.: Thomas, 1945. Price, \$5.00.

An anthology that includes in 200 pages the writings of more than 100 medical poets, extending over 1000 years (nearer 2000, if the translation of Lucretius is included), must indeed have taken the compiler through many libraries in a search extending over a number of years. Beginning with Wang Wei (699-759) of the T'ang Dynasty (whose 2 little gems are, to be sure, not medical poetry), the anthology takes us to the 16th century with but two stops—the well-known "The Salerne School doth by these lines impart all health to England's King" (ca. 1101), and an excerpt from Fracastoro's "Syphilis." In the next 2 centuries, the British dominate—here we find such well-known writers as Cowley, Garth, Arbuthnot, Smollett, Akenside, Goldsmith, Erasmus, Darwin, together with Redi and Schiller. With John Kearsley Mitchell and Walter Channing, Americans make their appearance; from then on they are more than twice as numerous as all the rest. We find no explanation of this obvious disproportion; nor can we agree with a number of Mrs. McDonough's selections which serve chiefly to sustain the quotation from Dr. John Fallon that much of the poetry written by physicians is "poetry in quotation marks and much of it is feeble stuff." Not that there is nothing worthy in these later selections. One misses Zinsser's exquisite sonnet "Now is death merciful," but one finds much to support Merrill Moore's assertion that most of the best poems in the tradition of medical literature are included. The Index of Authors is followed by a longer Cumulative Index of Poet Physicians. This contains many persons whose work one would have liked to have seen included: Aurelianus, Avicenna, Bartholinus, Claude Bernard, Gentile, Haller, Harvey, Helmont, Hippocrates, Imhotep, and so on. But perhaps when much that is good has been provided, it is unseemly to express a wish for more.

E. K.

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### NEW BOOKS

*Manual of Clinical Mycology.* Prepared under the Auspices of the Division of Medical Sciences of the National Research Council. By NORMAN F. CONANT, Ph.D., Assistant Professor of Bacteriology, Duke Univ. School of Medicine, and Mycologist to Duke Hosp. et al. Pp. 348; 148 figs. Philadelphia and London, Saunders, 1944.

*Neuro-ophthalmology.* By DONALD J. LYLE, B.S., M.D., F.A.C.S., Lecturer on Neuro-ophthalmology, Department of Anatomy, Medical College of the Univ. of Cincinnati; Attending Ophthalmologist to the Good Samaritan Hosp., Christ Hosp., Jewish Hosp., St. Mary's Hosp. and Children's Hosp. Pp. 398; 7 charts; 529 ills. Springfield: Thomas, 1945. Price, \$10.50.

- Poet Physicians.* An anthology of Medical Poetry Written by Physicians. Compiled by MARY LOU McDONOUGH. Pp. 210. Springfield: Thomas, 1945. Price, \$5.00.
- Immuno-catalysis.* By M. G. SEVAG, PH.D., Assistant Professor of Biochemistry in Bacteriology, Department of Bacteriology, School of Medicine, Univ. of Pennsylvania, Philadelphia. With a Preface by STUART MUDD, M.A., M.D., Professor of Bacteriology, School of Medicine, Univ. of Pennsylvania, Philadelphia. Pp. 272. Springfield: Thomas, 1945. Price, \$4.50.
- Modern Methods of Amputation.* By EDMUNDO VASCONCELOS, Professor, Univ. of Sao Paulo. With an Introductory Survey of The Development of Amputation by MAJOR GEN. NORMAN T. KIRK, M.C., Surgeon General, U. S. A. Pp. 253; 258 figs. New York: The Philosophical Library of New York, 1945. Price, \$10.00.
- Marihuana Problems in the City of New York.* Sociological, Medical, Psychological and Pharmacological Studies. By the Mayor's Committee on Marihuana. Pp. 220. Lancaster: The Jaques Cattell Press, 1944. Price, \$2.50.
- The Neurologist's Point of View.* Essays on Psychiatric and Other Subjects. By I. S. WECHSLER, M.D. Pp. 251. New York: Fischer. Price, \$3.00.
- Microbial Antagonisms and Antibiotic Substances.* By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers Univ.; Microbiologist, New Jersey Agricultural Experiment Station. Pp. 350; 34 figs. New York: The Commonwealth Fund, 1945. Price, \$3.75.
- The March of Medicine.* The New York Academy of Medicine Lectures to the Laity, 1944. Pp. 121. New York: Columbia Univ. Press, 1945. Price, \$1.75.
- An Introduction to Somatic Methods of Treatment in Psychiatry.* By WILLIAM SARGANT, M.A., M.B. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp., and ELIOT SLATER, M.A., M.D. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp. Pp. 171. Baltimore: Williams & Wilkins, 1944. Price, \$2.50.
- The Chemistry and Physiology of Hormones.* Publication of the American Association for the Advancement of Science. Edited by FOREST RAY MOULTON. Pp. 243. Washington, D. C.: American Assn. Advance of Sci., 1944. Price, \$3.50 (\$4.00).
- Trauma in Internal Diseases.* With Consideration of Experimental Pathology and Medicolegal Aspects. By RUDOLF A. STERN, M.D., Assistant Attending Physician, City Hosp., New York City. Foreword by FRANCIS CARTER WOOD, M.D., Director of Laboratories and Radiotherapy Department, St. Luke's Hosp., New York. Pp. 590. New York: Grune & Stratton, Inc., 1945. Price, \$6.75.

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#### NEW EDITIONS

- Tropical Medicine.* By SIR LEONARD ROGERS, K.C.S.I., C.I.E., LL.D., M.D., B.S., F.R.C.P., F.R.C.S., F.R.S., Major-General, Indian Medical Service, Ret.; Late Medical Adviser to the India Office, and Physician and Lecturer, London School of Tropical Medicine; Lecturer on Tropical Medicine, London School of Medicine for Women; Late Professor of Pathology, Medical College, Calcutta; and SIR JOHN W. D. MEGAN, K.C.I.E., B.A., M.B., Hon. D.Sc. (Queen's University, Belfast), Major-General, Indian Medical Service, Ret.; Late Medical Adviser, India Office and Lecturer, London School of Tropical Medicine; Formerly Director-General, Indian Medical Service; Formerly Director and Professor of Tropical Medicine, Calcutta School of Tropical Medicine and Hygiene. 5th Ed. Pp. 518; 2 colored plates and 87 text-figures. Baltimore: Williams & Wilkins, 1944.

*Clinical Roentgenology of the Digestive Tract.* By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, Univ. of Maryland; Assistant in Gastroenterology, Mercy Hosp.; Consulting Roentgenologist, Sinai Hosp. 2nd Ed. Pp. 769; 550 figs. Baltimore: Williams & Wilkins, 1945. Price, \$7.00.

*Approved Laboratory Technic.* By JOHN A. KOLMER, M.S., M.D., DR. P.H., Sc.D., LL.D., Professor of Medicine in the School of Medicine and the School of Dentistry, Temple Univ.; and FRED BOERNER, V.M.D., Associate Professor of Clinical Bacteriology, Graduate School of Medicine and Assistant Professor of Bacteriology, School of Medicine, Univ. of Pennsylvania; Bacteriologist, Graduate Hosp., Philadelphia. 4th Ed. Pp. 1017; 336 ills. New York: D. Appleton-Century, 1945. Price, \$10.00.

This well-known comprehensive text on clinical laboratory methodology has been heavily revised by the authors and four of their thirty collaborators. The general plan remains the same as previous editions. This edition appears at an opportune time to complement Dr. Kolmer's new (1944) "Clinical Diagnosis by Laboratory Methods" which is chiefly interpretive. A Spanish language edition of this revision is said to be in preparation.

*Textbook of Anæsthetics.* By R. J. MINNITT, Trinity College, Cambridge, M.D. (LIVERPOOL), D.A. (R.C.P. and S. ENG.), Lecturer in Anæsthesia, Univ. of Liverpool; and JOHN GILLIES, M.C., M.B., Ch.B. (EDINBURGH), D.A. (R.C.P. and S. ENG.), Consultant in Anæsthetics, Department of Health for Scotland. With a chapter on Local and Regional Analgesia by L. B. WEVILL, M.B., F.R.C.S. (EDIN.), Major, R.A.M.C. 6th Ed. Pp. 487; 199 figs. Baltimore: Williams & Wilkins, 1944. Price, \$7.00.

*Textbook of Abnormal Psychology.* By ROY M. DORCUS, Associate Professor of Psychology, Univ. of California at Los Angeles; and G. WILSON SHAFFER, Dean of the College of Arts and Sciences, Lecturer in Psychology, Professor of Health and Physical Education, Johns Hopkins Univ. 3rd Ed. Pp. 547. Baltimore: Williams & Wilkins, 1945. Price, \$4.00.

*Constitution and Disease. Applied Constitutional Pathology.* By JULIUS BAUER, M.D., Professor of Clinical Medicine, College of Medical Evangelists, Los Angeles; Formerly Professor of Medicine, Univ. of Vienna. 2nd Ed. Pp. 255; various ills. and diagrams. New York: Grune & Stratton, 1945. Price, \$4.00.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1945

## ORIGINAL ARTICLES

### THE THERAPEUTIC USE OF RADIOACTIVE PHOSPHORUS\*††

BY COMDR. SHIELDS WARREN (MC), USNR

BOSTON, MASS.

(From the Laboratories of Pathology of the Harvard Cancer Commission and of the New England Deaconess Hospital and the Department of Pathology, Harvard Medical School)

RADIOACTIVE phosphorus, first prepared by E. O. Lawrence and utilized by J. H. Lawrence and his associates for the therapy of leukemia<sup>7</sup> and polycythemia,<sup>6</sup> has been tested in several localities. It is still being used in a few places, in spite of the difficulty of obtaining it owing to present exigencies of the war. From two centers there have been reported large series of cases: Those followed by Lawrence and his colleagues at the Crocker Radiation Laboratory<sup>6,7,8</sup> and those treated at the Memorial Hospital, New York, by Kenney,<sup>5</sup> Craver,<sup>1</sup> and their associates. The present group consisting of 81 cases and begun in January 1940 constitutes the third large series to be reported.

Radioactive phosphorus as utilized in this series has been prepared in one of two ways: (1) the bombardment by the cyclotron of red phosphorus placed in the external target chamber, and (2) the bombardment of an iron phosphide probe placed in the deuteron stream of the cyclotron just inside the port.

The first method gives a product of relatively low specific activity; the second, one of high specific activity. By either method, only a fraction of the total phosphorus bombarded is rendered radioactive. Depending on the size of the cyclotron and whether the phosphorus is placed in the target chamber or on a probe, the necessary time of exposure to produce a given radioactivity will vary. It usually requires 6 to 8 hours of bombardment to obtain 25 millicurie equivalents of

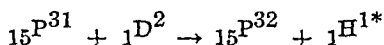
\* The major portion of this study was aided by grants from the International Cancer Research Foundation, a part by a grant from Eli Lilly & Co.

† For the radioactive phosphorus used in this study, I am indebted to Prof. Robley D. Evans of the Massachusetts Institute of Technology, to the Harvard Cyclotron Committee, and to Prof. Ernest O. Lawrence of the Crocker Radiation Laboratory.

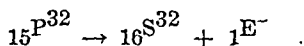
‡ This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

activity under favorable conditions. The phosphorus is converted by standard chemical procedures, first to phosphoric acid and then usually to dibasic sodium phosphate. Chemical manipulation has no effect on the radioactivity, the temporarily radioactive atoms reacting as would any phosphorus atom.

Radioactive phosphorus has a half life of 14.3 days; and, like all radioactive substances, has a steady rate of decay. The reaction of its formation is:



$\text{P}^{32}$  gives off an electron as beta radiation, thereby being converted to sulphur according to the following reaction:



While only one of many temporarily radioactive substances there are striking advantages in the use of radioactive phosphorus as a means of internal therapeutic radiation. Its half life is long enough to permit the necessary chemical manipulations to prepare it for administration without undue loss of activity; it is short enough to have no long-range harmful effects on the body. The beta rays given off have relatively low penetrating power (2 to 4 mm. of tissue). Certain cells, among them leukemic cells, preferentially absorb the material. The end-product of the reaction, sulphur, is not radioactive and is harmless.

**Methods.** The measurements of radioactivity were carried out on a modified Geiger-Muller counter, checked from time to time with a Lauritsen type electroscope. For the measurements of radioactivity, I am indebted to Mr. R. F. Cowing of this hospital. The energy of radioactive phosphorus is measured in millicurie equivalents; that is, the ionizing power of its beta radiation as compared with the ionizing effect on air of 1 millicurie of radon. It will be seen at once, owing to the different types of radiation involved (beta as against beta and gamma), that there can be no direct translation of biologic effectiveness from radioactive phosphorus to radon. It has been calculated that 0.1 microcurie of radioactive phosphorus per gram of tissue delivers about 355 ergs in the first 24 hours.<sup>6</sup> This has the ionizing effect of 4.2 roentgens of therapeutic Roentgen rays delivered per gram of tissue.

At first, we administered  $\text{P}^{32}$  as  $\text{Na}_2\text{HPO}_4$ ; then, as skilled chemical help became less abundant, magnesium ammonium phosphate ( $\text{MgNH}_4\text{PO}_4$ ) produced as a step in the preparation of sodium phosphate, was utilized and proved satisfactory. As a still further simplification, even  $\text{H}_3\text{PO}_4$  has been used when the lots have been of high specific activity, without a single untoward reaction.<sup>12</sup> We are indebted to Dr. John Irvine of M. I. T. for these latter forms.

As a rule, the desired dose of  $\text{P}^{32}$  was administered intravenously dissolved in 300 cc. of 0.85% NaCl and 5% glucose in the case of adults, and in 100 cc. of the same diluent in the case of infants and young children. Glass or rubber tubing of ordinary thickness absorbs a sufficient amount of radioactivity to render special precautions for the protection of personnel unnecessary during the brief period of handling. When the material is given orally, the dose is dissolved in 150 cc. of orange juice. With oral administration, 20 to 30% of the dose is not absorbed, owing largely to precipitation of a portion in the gastro-intestinal tract as insoluble phosphates.

\* This arrangement has been adopted by physicists to signify the atomic number in the subscript and the atomic weight in the superscript.—Ed.

We prefer the intravenous route for giving radioactive phosphorus since this entails accurate measurement of the dose absorbed, conservation of material and the rapid attainment of an adequate concentration in the blood stream. A limited number of cases have been treated with radioactive phosphorus by the oral route as a check against the intravenous method. In most cases, measurements of the concentration of radioactivity in whole blood and its various components were made.<sup>11</sup> The rate of excretion was also followed in the majority of the cases.

We have selected for  $P^{32}$  therapy those types of disease known to be highly radiosensitive—leukemia, lymphoma, plasmacytoma and Hodgkin's disease. However, we decided to limit the cases chosen for treatment chiefly to those which after initial favorable response to roentgen radiation have become resistant, and also to those cases of leukemia known commonly to do badly with Roentgen radiation as, for example, acute leukemia in childhood. A few moribund cases of chronic leukemia were treated partly to see if anything could be accomplished for them, partly to learn whether the effect of  $P^{32}$  varied from the usual in those cases with extremely high white blood cell counts and very low red blood cell counts. Because of the cases selected for therapy the results in this series will appear discouraging in the aggregate.

We based our decision to work with this relatively unfavorable group on several reasons. The efficacy of  $P^{32}$  therapy of chronic leukemia was being evaluated by the careful studies of Lawrence and others. Most cases of chronic leukemia will respond fairly well, at least temporarily, to Roentgen therapy. Particularly at the beginning of the study,  $P^{32}$  was difficult to obtain and the supply was somewhat uncertain. It hardly seemed fair to use the material under these conditions for patients who in all probability would do well with more readily available methods of treatment.

There is always discussion as to the classification of leukemias. We have endeavored to classify these cases according to accepted methods. In a few instances where there was a question of classification, blood smears and biopsies of lymph nodes or bone marrow have been submitted to several authorities. Four types of leukemia are included in the series: myelogenous, lymphatic, monocytic and plasma cell. We have attempted to distinguish 3 phases of activity of the leukemic process: acute, subacute and chronic, based upon the proportion of blasts present in the circulating blood and the clinical course of the patient. By no means can all the cases be readily pigeonholed in these groups and certain arbitrary standards were devised. If over 20% of the cells in the circulating blood were blasts at the time the case was first seen and during the initial days of therapy, it was regarded as subacute; if over 50%, acute. The acute cases were all febrile; the subacute cases were usually febrile. Petechiæ, purpuric lesions and hemorrhage from mucous membranes were considerably more frequent in the acute and subacute cases than in the chronic.

The cases were further divided into: (a) those treated with Roentgen radiation who had either failed to respond after a period of previous good response or proved to be resistant from the start; and (b) those



who had had no previous radiation therapy. There were 31 of the former and 50 of the latter.

TABLE 1.—RESULTS OF THERAPY

Type	Previous Roentgen ray therapy	Number of cases	Number helped	Per cent helped
Chronic myelogenous leukemia . . .	—	9	5	56
	+	10	4	40
Subacute myelogenous leukemia . . .	—	2	2	100
	+	0	0	0
Acute myelogenous leukemia . . .	—	8	0	0
	+	1	0	0
Chronic lymphatic leukemia . . .	—	3	1	33
	+	5	4	80
Subacute lymphatic leukemia . . .	—	2	0	0
	+	2	1	50
Acute lymphatic leukemia . . .	—	8	1	13
	+	4	2	50
Monocytic leukemia . . .	—	4	1	25
	+	0	0	0
Acute leukemia, unclassified . . .	—	8	0	0
	+	0	0	0
Lymphosarcoma . . .	—	2	0	0
	+	2	0	0
Plasma cell leukemia . . .	—	0	0	0
	+	1	0	0
Plasmacytoma . . .	—	0	0	0
	+	3	2	67
Hodgkin's disease . . .	—	0	0	0
	+	3	1	33
Polycythemia vera . . .	—	3	2	67
Blood dyscrasia, unclassified . . .	—	1	1	100
Total . . .		81	27	33

A total of 81 cases were treated in the period from January 1940 to September 1944 (see Table 1). Four (Cases 1 to 4) have been reported in part previously.<sup>9</sup> In this table the number of cases in each category and the number that were helped by the treatment are reported. Those cases were considered helped which showed definite clinical and laboratory evidence of improvement. Such a person regained a fair degree of former activity for a period of 3 months or more, the white blood cell count was significantly lowered with an increase in the proportion of mature forms present, and the temperature returned to normal. The basal metabolic rate, when determined, was lowered. The possibility of spontaneous remission must always be kept in mind, but in the great majority of these cases spontaneous remission would be most unlikely. The best results were obtained in previously untreated cases of chronic and subacute myelogenous leukemia, 7 of 11 showing improvement, and in lymphatic leukemia previously treated with Roentgen ray, 7 of 11 again showing improvement. The cases of leukemia in childhood in general did badly, although some promising leads were obtained. These cases, most of which were studied in collaboration with Dr. Louis K. Diamond, will be reported in detail later. Histories of representative cases are presented below.

**Case Histories.** CASE 7. R. K. *Chronic myelogenous leukemia, advanced but not terminal, previously untreated.*

Patient, a married white female, 45 years of age, entered the Peter Bent Brigham Hospital November 14, 1940, with a history dating back to 1934 when cholecystectomy was performed, followed by choledogastrostomy and subphrenic abscess, then for several years recurrent attacks of cholangitis with development of a biliary cirrhosis. In summer of 1940, she had severe left abdominal pain for 10 days (relieved by binder) followed by abdominal fullness and 20 pounds weight loss. Severe left upper quadrant pain 2 days before admission. Patient was moderately obese, with a few soft, palpable cervical nodes; spleen extended to right of and 10 cm. below umbilicus; friction rub and tenderness over spleen; liver 6 cm. below costal margin; slight edema of ankles. White blood cell count was 322,000, red blood cell count 3,550,000, hemoglobin 9.9 gm., neutrophils 40%, band forms 22%, myelocytes 33%, myeloblasts 2%, basophilic leukocytes 2%, eosinophils 1%. Sternal bone marrow biopsy showed myelogenous leukemia.  $P^{32}$  therapy (in the form of  $\text{NaH}_2\text{PO}_4$  dissolved in 0.85% NaCl and 5% glucose) started with 2260  $\mu\text{c}$ . intravenously on Nov. 20, 1940, then 2600  $\mu\text{c}$ . intravenously on November 30, which was followed by a chill. By December 29, the spleen was somewhat smaller and patient had improved clinically. Patient returned home and was readmitted Feb. 4, 1941, generally stronger; spleen 10 cm. and liver 2 cm. below costal margins; white blood cell count 44,000, red blood cell count 3,620,000, platelets normal; 3190  $\mu\text{c}$ .  $P^{32}$  intravenously given on Feb. 5, discharged condition unchanged. By March 20, white blood cell count 14,400, red blood cell count 3,930,000 and normal differential except for 7% myelocytes, basal metabolic rate +9, spleen extended 4 cm. down and liver not enlarged; 1000  $\mu\text{c}$ . intravenously given. White blood cell count varied between 6800 and 11,000 through July 1941; patient felt well and spleen was practically normal. On September 15 white blood cell count 27,000 with 70% band forms. General condition good, but spleen extended to umbilicus; 3500  $\mu\text{c}$ .  $P^{32}$  given intravenously. White blood cell count fluctuated between 36,000 and 71,000 until April 1942, with spleen extending below umbilicus and liver 6 to 10 cm. below costal margin. Received 2600  $\mu\text{c}$ . intravenously on Nov. 24, 1941, and 1500  $\mu\text{c}$ . on March 10, 1942. Readmitted on April 2, acutely ill, dyspneic, weak, with dullness in both lung bases, distended abdomen, spleen 8 cm. below umbilicus and liver 10 cm. below costal margin. White blood cell count 320,000 with 66% blasts, platelets normal. Received 1620  $\mu\text{c}$ .  $P^{32}$  intravenously on April 3 and 2140  $\mu\text{c}$ . on April 6. Patient died April 8 and autopsy (A-42-51) showed myelogenous leukemia involving heart, lung, spleen, liver, pancreas, kidneys, uterus, ovary, lymph nodes, bone marrow (chloroleukemia); pulmonary atelectasis; cerebral edema; biliary cirrhosis.

*Comment.* This was a favorable case that should have done better. The treatment was probably inadequate after February 1941.

CASE 60. F. Z. *Terminal chronic myelogenous leukemia, previously radiated and found resistant.*

Married white woman, 47 years of age. Developed symptoms of anemia in April 1941, and was found to have an enlarged spleen and chronic myelogenous leukemia. In spite of repeated Roentgen ray therapy her response was unsatisfactory and her white blood cell count remained well elevated. April 13, 1942, her white blood cell count was 250,000, her red blood cell count 3,770,000, hemoglobin 9.5 gm. Her differential count showed neutrophils 56%, band forms 12%, myelocytes 25%, myeloblasts 1%, lymphocytes 2%, eosinophils 2%, basophils 2%; platelets normal.

Her general condition was fair. The spleen occupied the entire left side of abdomen. On April 17, 1942, she was given 1800  $\mu\text{c}$ . intravenously without reaction. The basal metabolic rate was +34. April 23 she was given a second dose of 1800  $\mu\text{c}$ . intravenously, on May 12, 2700  $\mu\text{c}$ . intravenously, on July 8, 1400  $\mu\text{c}$ . intravenously, August 14, 2120  $\mu\text{c}$ . orally. Her general condition had materially improved, and the spleen had diminished to about two-thirds its former size. The white blood cell count had remained fairly high;

it did not go below 100,000. October 31 she was given 2800  $\mu$ c. orally and on November 21, 1800  $\mu$ c. She was active, doing her own housework and had no complaint except "heaviness" due to a prolapsed uterus. Jan. 5, 1943, she was given 3800  $\mu$ c. of radioactive phosphorus intravenously and on January 8, 1600  $\mu$ c. intravenously. The spleen was 3 cm. below the level of the umbilicus. The white blood cell count was 82,400, red blood cell count 3,830,000. February 9 she was given 1900  $\mu$ c. orally. March 11 she was given 1600  $\mu$ c. intravenously and March 12, 1800  $\mu$ c. intravenously. On April 22 she was given 2700  $\mu$ c. intravenously. Her general condition continued satisfactorily. Her white blood cell count at this time was 159,500, red blood cell count 4,070,000, hemoglobin 11.8 gm.; platelets normal. She continued doing fairly well until June 4. She had complained of some weakness and pain and numbness in right thigh. She was given 1800  $\mu$ c. orally. August 4 she had developed a marked anemia with a red blood cell count of 2,830,000, and on September 1 it had fallen to 1,960,000. She was given a 500 cc. transfusion of citrated blood. Her general condition deteriorated rapidly and it became apparent that further therapy would be useless. November 6 she died. Diagnosis: chronic myelogenous leukemia.

*Comment.* This case was one which had failed to respond satisfactorily to Roentgen therapy and was virtually moribund when treatment was attempted. She was given rather light doses of radioactive phosphorus at first and responded well clinically, maintaining a satisfactory red blood cell count and being able to go about her normal duties. Her white blood cell count never reached satisfactorily low levels and her spleen remained considerably enlarged in spite of her general improvement. After 15 months she developed a rapidly progressive anemia. This case had a year and a quarter of activity added to her life although there was never adequate control of the leukemia by radioactive phosphorus.

CASE 63. E. B. *Terminal chronic lymphatic leukemia.*

Patient, a married white male, 49 years of age, entered New England Deaconess Hospital June 4, 1942, complaining of enlarged lymph nodes of 2½ months duration and gradually increasing weakness for some months previously. He had recently received two 500 cc. citrated blood transfusions at the Boston City Hospital. Examination showed axillæ filled with hard, discrete, rounded nodes up to 10 cm. in diameter. Scattered, somewhat smaller nodes in both groins and numerous firm nodes up to 3 cm. in diameter in the neck, particularly on the left. Basal metabolic rate +50; white blood cell count 296,000, red blood cell count 4,030,000, hemoglobin 12.3 gm. Differential count at this time was: neutrophils 3%, lymphocytes 75%, young lymphocytes 21%, eosinophils 1%, blood platelets markedly decreased.

June 6, 1942, the patient was given 3900  $\mu$ c. of radioactive phosphorus intravenously followed on June 18 by 1800  $\mu$ c. and on June 26 by 3000  $\mu$ c. intravenously. July 27 he was given 600  $\mu$ c. of radioactive phosphorus intravenously. His white blood cell count was 28,950, hemoglobin 13.9 gm. His lymph nodes had decreased materially in size, his general condition was satisfactory, and the patient had returned to work as a janitor.

September 12, 1942, he was given 1500  $\mu$ c. of  $P^{32}$  orally and on October 31, 3500  $\mu$ c. orally and on December 5, 2300  $\mu$ c.  $P^{32}$  orally. On March 27, 1943, he received 1800  $\mu$ c. intravenously. Cervical nodes were now barely palpable. There were 2 nodes about 3 cm. in diameter in the left axilla. The lower pole of the spleen was palpable. His white blood cell count was 97,000; hemoglobin 14.8 gm. June 5 he was given 1880  $\mu$ c. radioactive phosphorus intravenously and September 4, 3200  $\mu$ c. intravenously; October 2, 2000  $\mu$ c. orally. This latter time the right inguinal nodes were somewhat enlarged. Patient was working steadily.

Feb. 5, 1944, patient was given 3000  $\mu$ c. orally. There were nodes in the cervical region and in both groins up to 1 cm. in diameter. The lower border of the liver was at the umbilicus. The spleen extended 5 cm. below the costal margin. The abdomen contained some fluid and there was a palpable epigastric mass. March 10, patient was given 1800  $\mu$ c. intravenously and on June 17, 4300  $\mu$ c. orally. August 19 patient received 2200  $\mu$ c. orally. Felt well, and had been working steadily for more than 2 years. Spleen extended to the anterior superior iliac spine and to the midline. White blood cell count was 172,000; hemoglobin 14.5 gm.

*Comment.* This is an advanced case of chronic myelogenous leukemia that experienced practically complete relief of symptoms and showed marked regression of leukemic enlargement of lymph nodes, liver and spleen. He has been able to work steadily and has maintained a satisfactory red blood cell count and hemoglobin with fair control of the white blood cell count. The past few months his white blood cell count has risen in spite of fairly heavy therapy.

CASE 51. P. G. *Acute monocytic leukemia.*

A white married male, 31 years of age, was admitted to the New England Baptist Hospital, Dec. 4, 1941, with history of progressive weakness, anorexia, dyspnea and 10 pounds weight loss for 2 months. Patient appeared cachectic, with sallowness and numerous small nodes in cervical, postauricular and axillary regions. Liver 4 cm. below costal margin. White blood cell count 6500, red blood cell count 2,690,000, hemoglobin, 7.05 gm., neutrophils 3%, band forms 6%, lymphocytes 39%, monoblasts 50%, young lymphocytes 2%, platelets 164,000, reticulocytes 0.3%. Sternal biopsy showed acute leukemia. Started on  $P^{32}$  therapy Dec. 5, with 2760  $\mu$ c. intravenously, then 2900  $\mu$ c. intravenously on December 13 (the latter followed by slight chill and nausea). Symptomatically the patient was somewhat improved and was discharged December 15, but was readmitted December 24 critically ill, with palate and uvula ulcerated, clotted blood on gums, scattered petechiae and the spleen palpable. White blood cell count 3500, red blood cell count 1,760,000. Received 615  $\mu$ c.  $P^{32}$  intravenously on December 26. Patient's course continued rapidly downhill with white blood cell count 3500 and red blood cell count 1,550,000 on December 30 (despite 4 transfusions). Differential count on December 29: neutrophils 1%, band forms 1%, lymphocytes 14%, atypical cells 15%, monoblasts 69%. Patient died Jan. 1, 1942.

*Autopsy* showed acute monocytic leukemia with infiltration of heart, lung, trachea, gums, spleen, pancreas, liver, adrenal, intestine, stomach, appendix, kidneys, prostate, testes and skin; hypoplasia of bone marrow; lipid histiocytosis of spleen; ulcerated and necrotic lesions of lips and gums; foci of cystic degeneration of brain.

*Comment.* This fulminating case of acute monocytic leukemia showed no response to therapy.

CASE 61. J. C. *Acute leukemia (unclassified).*

This patient, white male, 3 years of age, was a characteristic case of acute leukemia in childhood with petechial hemorrhages and enlarged lymph nodes. Patient was febrile, acutely ill, and anemic. April 21, 1942, patient was admitted to Children's Hospital with white blood cell count 7750, red blood cell count 1,860,000, hemoglobin 6.6 gm.; platelet count 44,000. Differential count showed blasts 60%, neutrophils 2%, lymphocytes 18%, monocytes 2%, eosinophils 2%, myelocytes 16%.

He was given 3 transfusions, and beginning April 28 he was given 5 daily doses of  $P^{32}$  intravenously, totaling 1300  $\mu$ c. He was transfused on May 4 and 5. On May 12 he showed a white blood cell count of 4750, red blood cell count of 4,070,000, hemoglobin 9.5 gm. Blasts had dropped to 26%. Begin-

ning May 13 he was given 1800  $\mu\text{c.}$  intravenously in 3 daily doses. On June 1 he was given 1000  $\mu\text{c.}$  divided into 2 portions. He rapidly lost ground and died June 7, 1942.

*Autopsy* showed extensive leukemic infiltration of various organs with some hypoplasia of leukemic bone marrow.

*Comment.* This was a case of acute, rapidly progressive leukemia in childhood. The course of the disease was not altered by therapy.

CASE 47. B. S. *Plasma cell myeloma.*

The patient, a single white female, 66 years of age, entered the Evans Memorial unit of The Massachusetts Memorial Hospitals, Nov. 10, 1941, with poor healing of dental incisions of gum and gave a history of vague pain, anemia and lethargy of about 1 year's duration. Roentgen ray studies showed the whole skeleton to be extensively involved with multiple myeloma. The liver was 10 cm. below costal margin. The red cell count was 2,300,000; the white blood cell count was 8450, with 6% plasma cells; platelets 218,000, serum protein 10.02%. Sternal puncture showed masses of plasma cells.

She received 1950  $\mu\text{c.}$  radioactive phosphorus intravenously Nov. 12, 1942, and 2500  $\mu\text{c.}$  intravenously November 21. The bone pain disappeared promptly. By the time of her discharge from the hospital on November 25 the macrocytosis had decreased from 120 to 95 c. $\mu$ . She showed subjective improvement and on Dec. 22, 1941, was given 2140  $\mu\text{c.}$  intravenously. On January 21, 1942, she received 2140  $\mu\text{c.}$  intravenously and on February 19 she received 2200  $\mu\text{c.}$  At this time her basal metabolic rate was +13. She had some headache. April 14 she was given 1150  $\mu\text{c.}$  intravenously. Roentgen examination showed some recalcification of the osteolytic foci. The red blood cell count was 4,300,000, hemoglobin 12.3 gm., white blood cell count 5600. She had been suffering from hypertension and developed rational hemorrhages in July 1942.

She was readmitted September 24, and received 1600  $\mu\text{c.}$  intravenously. This time her red blood cell count was 4,200,000, her white blood cell count 5800 with 70% neutrophils, and no plasma cells. The platelet count was 552,000; the serum protein 8.76% with albumin-globulin ratio of 0.86:1. Aside from hypertension she was doing well.

Patient was readmitted Feb. 9, 1943, in poor condition. She had had several severe nosebleeds and bone pain reappeared. Her red blood cell count was 1,800,000 and the serum protein 9.46% with albumin-globulin ratio of 0.46:1. Roentgen examination of the bones showed no change. She was given 2300  $\mu\text{c.}$  of  $\text{P}^{32}$  intravenously. On March 10 the red blood cell count was 1,630,000. Investigation of recent digestive difficulties showed an active duodenal ulcer. March 25 she was given 2 transfusions each of 500 cc. citrated blood and 1830  $\mu\text{c.}$  of  $\text{P}^{32}$  was given intravenously. Her general condition improved markedly and remained satisfactory for about 2 months, then her weakness returned.

On July 31, 1943, she was given 3940  $\mu\text{c.}$  radioactive phosphorus intravenously. Her red blood cell count was 2,400,000 following 3 transfusions. In September her condition had become serious with weight loss and weakness. She was readmitted to the hospital September 15 and after 5 transfusions her red blood cell count reached 2,010,000. November 16 she was readmitted critically ill with pneumonia of 1 week's duration. Her white blood cell count was 1550, red blood cell count 1,630,000. Her non-protein nitrogen was 65 mg. per 100 cc. She died Nov. 20, 1943.

*Autopsy* showed multiple myeloma of almost all bones involving also lymph nodes, liver and kidneys. Immediate cause of death was lobar pneumonia.

*Comment.* This case of multiple myeloma showed appreciable improvement lasting from November 1941 to February 1943. Her condition was complicated by hypertension, nephritis, and terminal lobar

pneumonia. No permanent control of the myeloma was achieved, although its extent was retarded.

CASE 45. S. D. *Polycythemia vera*.

The patient, a single white female, 44 years of age, was admitted to the New England Deaconess Hospital Nov. 25, 1941. She had noticed an increasingly ruddy complexion becoming purple when cold, frequent headaches, and intermittent leg pains. Physical examination was negative except for ruddy color.

Her red blood cell count was 8,680,000, hemoglobin 18.15 gm., reticulocytes 1.2%. Her white blood cell count was 23,950 with 80% polymorphonuclear leukocytes; platelets, 694,000. Nov. 26, 1941, the patient received 3000  $\mu$ c. radioactive phosphorus intravenously. On Jan. 13, 1942, her red blood cell count was 7,550,000, white blood cell count 8750. She showed no reticulocytes. She was given 1940  $\mu$ c. of  $P^{32}$  intravenously. She had become symptom-free by this time and since then has had no difficulty. On March 30, 1942, her red blood cell count was 6,330,000 with 0.5% reticulocytes. Her white blood cell count was 8750. She was given 1200  $\mu$ c. of radioactive phosphorus. July 8 her red blood cell count was 4,520,000; her hemoglobin was 12.6 gm.

She has had no further symptoms and no treatment was given until June 5, 1943. At this time her red blood cell count was 5,980,000. She was given 1240  $\mu$ c. of  $P^{32}$  intravenously. March 10, 1944, she was symptom-free with a red blood cell count of 5,980,000; hemoglobin of 16.35 gm. She was seen May 9 with no symptoms from polycythemia but some pain in the left ankle which cleared promptly with rest.

*Comment.* This patient was relieved of her symptoms a month following her first injection of radioactive phosphorus and has had no recurrence of them in nearly 3 years. We have allowed her red blood cell count to remain a little high. Her disease has been readily controlled with moderate doses of radioactive phosphorus at long intervals.

*Discussion.* On the basis of the foregoing cases two facts become apparent. First, no harm has been done by the administration of radioactive phosphorus in the doses used. Second, a limited number of cases have done better than would be expected with the ordinary means of therapy. Much hinges on the extent of involvement of the bone marrow by the leukemic process when therapy is undertaken. If there is extensive leukemic infiltration of the marrow and very little normal hematopoiesis, nothing is to be gained by treatment aimed at wiping out the leukemic cells. One will be simply in effect changing a leukemia into an aplastic anemia. Hence a sternal bone marrow aspiration or biopsy is desirable in assessing a case being considered for  $P^{32}$  therapy.

That therapeutic doses of radioactive phosphorus do not appreciably damage normal red cell formation is shown by several of the cases which had rapid and well-defined increases in red blood cell count at a time when the white count was dropping following administration of the material. Of interest in this connection is the fact that a similar or smaller dose used in the therapy of polycythemia vera may induce a marked and rapid drop in red cell count.

Apparently if there is some normal marrow left behind, even heavy dosages of radioactive phosphorus will not do permanent harm. Thus in Case 21 very heavy dosage was used in a desperate attempt to ameliorate her condition. The total white count was dropped to a level of

350 but there was a prompt improvement from this low level and the patient had a remission of some months duration following this course of therapy. Therapy of so drastic nature is not to be recommended, however, and is cited simply to show that even heavy dosage will not produce complete destruction of all granulopoietic tissue.

Interestingly enough, the megakarocytes are apparently relatively unharmed by the dosage used and frequently an increase in platelet count follows therapy with radioactive phosphorus. In Case 23, the increasing platelet count was a guide to the beginning of the remission and a falling platelet count antedated the clinical and hematologic recrudescence of the leukemic process.

The basal metabolic rate is one of the useful guides to progress of the disease. This shows to an appreciable degree the activity of the leukemic process and may be an even better index at times during the period of therapy than is the peripheral white blood cell count, which may remain low while the leukemic process is active in the tissues. In several of the cases in the present series, the failure of appearance of a significant decrease in the basal metabolic rate was indicative of the later unfavorable course.

Radiation sickness was encountered only in 1 case (No. 48), even though many of the cases treated had previously been made severely ill by Roentgen radiation. In the early stages of the work, febrile reactions occurred with some of the cases where the specific activity of  $P^{32}$  was low and where a sufficient degree of purification of the  $Na_2HPO_4$  had not been carried out. With material of higher specific activity or with adequate purification, no febrile reactions have been noted. One patient (Case 48) complained of nausea following treatment and refused further therapy.

Studies of distribution of radioactive phosphorus in the tissues of these leukemic patients and of its partition in the blood in general confirm the results reported by Erf<sup>2</sup> and others.<sup>3,4,10</sup> Owing to the ready diffusibility of the phosphate ion,  $P^{32}$  permeates all the body tissues and fluids but varies strikingly in its concentration. Leukemic tissue picks up a considerably higher concentration of  $P^{32}$  than normal tissues.

During the first few hours after the administration of  $P^{32}$  it remains in fair concentration in the blood plasma but is readily taken up by the blood cells and the tissues. After some hours much of  $P^{32}$  present in the blood stream is in the leukocytes with very little in the plasma and a fair amount in the red cells. Thus in Case 32 an injection of 2120  $\mu$ c. radioactive phosphorus showed at the end of 2 hours 2.25  $\mu$ c. per 100 cc. of plasma, 11.3  $\mu$ c. per 100 cc. of red cells, 22.5  $\mu$ c. per 100 cc. of white cells. At the end of 24 hours there was 0.7  $\mu$ c. per 100 cc. of plasma, 12  $\mu$ c. per 100 cc. of red cells, and 22  $\mu$ c. per 100 cc. white cells.

At the end of 3 days about 75% of the intravenously administered dose is retained in the body, and 50% at the end of a week.<sup>3,12</sup> The proportion retained is fairly constant.

While the degree of leukemic infiltration of a given tissue largely influences the amount of  $P^{32}$  absorbed, certain tissues tend to concentrate the material. The liver, the kidneys, the spleen, the bone marrow show proportionately large amounts, while cartilage, fat and brain show little. After some days, the concentration in bone itself increases relatively.

Soon after administration saliva contains an amount almost comparable to that in the blood, and this gradually disappears. The normal spinal fluid does not attain a concentration approaching that of the blood until a number of days have passed, when the amount in the blood is low. Bile, particularly several days after injection, may contain larger amounts than does the blood owing to the selective deposition of  $P^{32}$  in the liver.<sup>10</sup>

Practically all radioactive phosphorus administered intravenously is excreted by the kidneys. If administered orally, up to 25% may be recovered from the feces, but this is chiefly material which has been precipitated as insoluble phosphates and not absorbed rather than actual excretion. The presence of appreciable amounts of  $P^{32}$  in the feces when the material has been administered intravenously indicates either hemorrhage into the intestinal tract or fairly extensive leukemic infiltration of the mucosa.

**Summary and Conclusions.** 1. Eighty-one cases of leukemia, myeloma, Hodgkin's disease and polycythemia vera have been treated with radioactive phosphorus.

2. Most of the cases had failed to respond to or were known to be refractory to Roentgen therapy or were far advanced.

3. Radioactive phosphorus provides a safe means of internal radiation, somewhat selective, of leukemic tissue.

4. The treatment is palliative rather than curative.

5. It may be temporarily effective in some cases that no longer respond to Roentgen therapy.

6. It is useless when but little normal hematopoietic tissue remains.

7. Radioactive phosphorus rarely produces radiation sickness.

8. About one-third the cases treated showed temporary improvement.

I am indebted to Drs. William B. Stevens, Louis K. Diamond, Joseph F. Ross and William Dameshek for aid in the clinical management of many of the cases reported here; and to Mr. Russell F. Cowing for determinations of radioactivity.

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# RADIOACTIVE PHOSPHORUS IN THE TREATMENT OF POLYCYTHEMIA VERA

## RESULTS AND HEMATOLOGIC COMPLICATIONS\*

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RADIOACTIVE phosphorus, supplied through the courtesy of Dr. J. H. Lawrence of the University of California, has been employed by us as a therapeutic agent in 12 cases of polycythemia vera in 2½ years. It is the purpose of this paper to report the results obtained and the complications encountered with this type of therapy.

**Dose and Method of Administration.** The intravenous method of administration was employed. The initial dose varied from 4 to 7 mc. in the majority of cases, and second or third injections were given during ensuing weeks whenever the material was available. As circumstances beyond our control prevented us from obtaining radioactive phosphorus at regular intervals, the treatment in some cases was inadequate.

Of the 12 patients treated with radioactive phosphorus, 7 were men and 5 were women. They ranged in age from 41 to 73 years. Of the 12 patients, 11 were known to have had the disease for from 6 months to 13 years and each had been treated by other means (venesection, oral administration of phenylhydrazine, or Roentgen irradiation over the spleen and bones) prior to administration of radioactive phosphorus. The diagnosis in the remaining case was made 2 weeks before administering the substance. In this case, 1500 cc. of blood was withdrawn in 2 weeks.

During the periods the patients were under observation, examinations of the blood were made at intervals of 1 month, and on recurrence of the polycythemia additional radioactive phosphorus was administered. In a few instances, when the material was not available, it was necessary to revert to other methods of treating the disease. The period of observation after treatment with radioactive phosphorus was started varied from 5 to 26 months.

**Results.** Satisfactory remissions were induced in 8 of the 12 cases and incomplete remissions occurred in 2 cases. In the 2 remaining cases the results were unsatisfactory owing, we believe, to inadequate treatment (Table 1).

TABLE 1.—RESULTS OF TREATMENT OF POLYCYTHEMIA VERA WITH RADIOACTIVE PHOSPHORUS

Results	Cases
Satisfactory remission . . . . .	8
Improved; remission incomplete (dose probably inadequate) . . . . .	2
Unsatisfactory (dose inadequate) . . . . .	2

\* Read by title at the meeting of the Association of American Physicians in Atlantic City, May 9, 1944.

† Since this work was undertaken, Dr. Watkins has entered the armed forces and is now a Captain (MC) USNR.

In the group in which satisfactory remissions were induced, both clinical and hematologic improvement was noted. Complete relief of symptoms attributable to the polycythemia occurred. Up to the time of the present writing, the remissions have lasted from 8 to 26 months. Six of the remissions have had a duration of more than 1 year.

Considerable variation in the doses required to induce satisfactory remissions were noted in this group (Table 2). In the average case of polycythemia vera, Lawrence and his associates<sup>4</sup> originally recommended doses of 14 mc., given in 2 equal injections 3 weeks apart of 7 mc. each. However, it was found that in many cases of polycythemia vera, presumably in cases of milder forms of the disease, smaller doses produced a satisfactory response. In Case 4, in which the patient, a woman 41 years of age, who had had polycythemia vera in mild form for 5 years, there was a remission that lasted 16 months after a single injection of only 4 mc. of radioactive phosphorus. In Case 5, in which the patient was 73 years of age, and who also had mitral stenosis and recurrent attacks of congestive heart failure, definite improvement was produced by the administration of 5 mc. of the substance. On the other hand, the patient who obtained a remission of 26 months duration (Case 1) received a series of 3 injections in a period of 2 months the dose totalling 13 mc. A fourth injection of 2.68 mc. was given 16 months after the third injection even though the polycythemia had not recurred.

TABLE 2.—TREATMENT OF POLYCYTHEMIA VERA WITH RADIOACTIVE PHOSPHORUS (P<sup>32</sup>)

Case	Courses of treatment	No. of injections	Dosage (mc.)	Total dosage (mc.)
1*	1	3	13.00	
	16 mos. later	1	2.68	15.68
2*	1	2	14.00	14.00
3*	1	1	7.00	7.00
4*	1	1	4.00	4.00
5*	1	2	5.00	5.00
6*	1	2	9.36	9.36
7*	1	3	10.60	10.60
8*	1	1	7.05	
	2 mos. later	1	5.25	12.30
9†	1	1	6.00	
	5 mos. later	1	6.60	12.60
10†	1	2	14.00	
	17 mos. later	1	6.40	20.40
11‡	1	1	4.76	
	9 mos. later	1	6.05	10.81
12‡	1	1	2.02	2.02

Character of remission: \* Satisfactory.

† Incomplete (clinical improvement).

‡ Unsatisfactory.

In the 2 cases in which the remissions were incomplete, definite clinical improvement was noted but the polycythemia, although improved, was not completely and adequately controlled. Both patients had severe forms of the disease. In Case 9, an initial injection of 6 mc. was given and 5 months later a second injection of 6.6 mc. was administered. Although the erythrocyte count dropped to 5,400,000

per c.mm. 1 month after the second injection, it rose to 7,800,000 4 months later, necessitating the use of venesections to control the disease. In Case 10, an initial course of 14 mc. was given. Five months later the erythrocyte count was 5,680,000 and the hematocrit value was 59%. One month later the erythrocyte count rose to 7,660,000 and it was necessary to employ repeated venesections to control the disease. Nineteen months after the first course of radioactive phosphorus was given, an additional 6.4 mc. was administered. Sufficient time after the last injection of radioactive phosphorus has not elapsed to determine what effect this will have on the disease. The total dose administered to this patient amounted to 20.4 mc.

In the group in which remissions were not obtained there were 2 cases (Cases 11 and 12). In Case 11 the patient was a woman, aged 59 years, who had had the disease in severe form for 13 years. An initial injection of 4.76 mc. did not affect the course of the disease materially and resumption of therapy by means of venesection and the oral administration of phenylhydrazine hydrochloride was carried out. Nine months later an injection of 6.05 mc. was given, but sufficient time has not elapsed after the second injection to allow conclusions to be drawn concerning the effect of the substance on the disease. In Case 12 the patient received only 2.02 mc., a dose we believe to be totally inadequate for the patient. This dose did not significantly alter the course of the disease.

**Complications.** No toxic reactions developed in any of the cases in which radioactive phosphorus was administered. Radiation sickness did not occur. However, hematologic complications in the form of anemia, leukopenia and thrombocytopenia were noted in several cases and acute leukemia developed in 1 case (Table 3).

TABLE 3.—HEMATOLOGIC COMPLICATIONS OF TREATMENT OF POLYCYTHEMIA VERA WITH RADIOACTIVE PHOSPHORUS ( $P^{32}$ )

Complications	Cases	Months after administration	Hematologic data*
Anemia . . . . .	5	2-25	Hemoglobin: 9.8-10.9 gm. Erythrocytes: 3,400,000-4,000,000
Leukopenia . . . . .	5	$\frac{1}{2}$ -6	Leukocytes: 2200-4300 (less than 4000 in only 2 cases)
Thrombocytopenia . . . . .	4	1-2	Platelets: 29,000-86,000
Acute leukopenic myelogenous leukemia	1†	16	Hemoglobin†: 6 gm. Erythrocytes: 2,000,000 Leukocytes: 1200 Platelets: 9000 Myeloblasts: 8%

\* The values for hemoglobin are for 100 cc. of blood; those for erythrocytes, leukocytes and platelets per cubic millimeter of blood.

† Hematologic data at time of last dismissal from clinic.

Anemia was observed in 5 cases, and was found to be of the hypochromic or normochromic, normocytic types. In 1 case it developed 2 months after administration of the last injection of radioactive phosphorus; in the other 4 it occurred in from 7 to 25 months after the

administration of the substance. In all cases it was mild and of relatively transient duration.

Leukopenia was encountered in 5 cases also, but in only 2 cases was the leukocyte count found to be less than 4000 cells per c.mm. In 1 case the leukocyte count fell to 2200 two weeks after the last injection of radioactive phosphorus had been given; in the other case, it dropped to 3600 three weeks after administration of the material. The leukopenia was of short duration in all cases, and there were no serious complications as a result of it.

Thrombocytopenia occurred in 4 cases, the platelet counts varying from 29,000 to 86,000 per c.mm. The only hemorrhagic phenomenon observed was the development of petechiæ on the lower extremities in 2 cases. These disappeared in the course of a few weeks as the platelet counts gradually rose.

One patient (Case 3) is of particular interest because he died with the blood picture of acute leukopenic myelogenous leukemia after having a remission of 13 months. This patient was a 63 year old man who had had symptoms attributable to the polycythemia for  $3\frac{1}{2}$  years prior to the administration of radioactive phosphorus. He received 1 injection of 7 mc. 18 months before death occurred. Thirteen months after administration of radioactive phosphorus, his family physician had found that the erythrocyte count was high and had withdrawn 1000 cc. of blood. Six weeks later the patient complained of blurring of vision and a sensation of pressure in his head, and returned to the clinic for reexamination. The values for the hemoglobin, the erythrocyte count and the hematocrit reading were normal; the leukocyte count was 4400 per c.mm. and examination of the blood smears revealed no abnormalities aside from signs of a slight increase in regeneration of erythrocytes. He was sent home, but returned 2 months later, only 2 months before death, complaining of marked weakness and dyspnea on exertion. One week previously he had noted "tarry" stools and had continued to pass black stools for 3 days. Examination disclosed marked pallor and a few scattered petechiæ on the lower limbs. The axillary lymph nodes were moderately enlarged; the spleen and liver were approximately the same size as they had been at the time of his previous visits to the clinic. The value for the hemoglobin was 5.5 gm. per 100 cc. of blood, the erythrocyte count was 2,010,000, the leukocyte count was 1600 and platelet count was 40,000. Examination of blood smears showed abundant myeloid immaturity. Myeloblasts were comparatively numerous, many containing Auer bodies. It was concluded that an acute leukopenic myelogenous leukemia had developed as a terminal event in a case of long-standing polycythemia vera.

The fact has long been recognized that polycythemia vera may terminate with the clinical and hematologic picture of chronic myelogenous leukemia; but the development of an acute leukemia terminally is unusual. From a theoretical viewpoint the possibility of a causal relationship between the administration of radioactive phosphorus and the occurrence of acute leukemia should be given consideration, but

such a relationship does not seem likely for 2 reasons: (1) the first definite signs of leukemia developed long after the material had lost its radioactivity except for an infinitesimally small quantity, and (2) signs of leukemia did not appear in other patients receiving treatment over considerably longer periods of time.

**Comment.** The results in this series of cases compare favorably with those in the literature. Low-Beer, Lawrence and Stone<sup>4</sup> observed partial or complete remissions in 11 of 14 cases of polycythemia vera; the remissions lasted from several months to 2 years. Fitz-Hugh and Hodes<sup>2</sup> noted marked improvement in 4 of 8 cases, slight improvement in 1 case, but no improvement in 1. In the 2 remaining cases the patients had not been treated a sufficient length of time to warrant comment. Erf and Jones<sup>1</sup> reported satisfactory remissions in 11 cases, and Hemplemann and his associates<sup>3</sup> in a preliminary report on the hematologic complications of radioactive phosphorus therapy, stated that they had treated 7 patients with this disease, but the results obtained were not discussed in the paper.

Excluding Hemplemann's cases because the details of treatment are not yet available, the effect of treatment with radioactive phosphorus has been reported in 33 cases. This number together with the 12 cases which we have reported, totals 45 cases in which radioactive phosphorus has been employed. Partial or complete remissions were observed in 37 of the 45 cases. Of the 8 remaining cases, 2 had not been observed a sufficient length of time to warrant comment, in 2 cases the therapy had not been adequate, and in 4 cases the patients were not improved.

On the basis of the reports in the literature and our own experience, it is our impression that the effectiveness of radioactive phosphorus in the treatment of polycythemia vera is well established. Patients obtaining satisfactory remissions not only obtain complete relief of symptoms attributable to the polycythemia vera, but they do not require any other type of therapy during the period of the remission. On the other hand, in cases in which partial or incomplete remissions occur, some other type of therapy may be required to control the disease satisfactorily, at least until an adequate supply of radioactive phosphorus is available. We would like to emphasize that the dose of radioactive phosphorus must be individualized for each patient. Patients with a mild form of the disease require much smaller dosages than do those with severe polycythemia vera. Periodic examinations of the blood are essential throughout the period of the remission, and with recurrence of the polycythemia, additional radioactive phosphorus should be given.

It is thought that the action of radioactive phosphorus is similar to that of Roentgen therapy of the bone marrow, both types of irradiation resulting in destruction of the cells. Marshak<sup>5,6</sup> has presented evidence indicating that Roentgen irradiation decreases erythropoiesis by retarding mitosis of normoblasts in early prophase. In any event, it seems more logical to employ an agent which acts directly on the bone marrow by diminishing erythropoiesis than to utilize methods which stimulate the marrow to form more cells, as phenylhydrazine

therapy and venesection both do. Although complications in the form of leukopenia, thrombocytopenia or anemia may occur with internal radiation therapy, serious damage to the bone marrow can be averted by frequent and careful hematologic studies. The advantages of this type of therapy seem to outweigh the slight risk involved.

**Conclusions.** In conclusion, on the basis of reports of other authors and our own experience, we feel that the effectiveness of radioactive phosphorus as a therapeutic agent in polycythemia vera is well established. This type of treatment is in no way curative; but the disease can be more readily controlled with internal radiation than with any other therapeutic procedure now available. Remissions lasting from 9 to 26 months were observed in our cases. The results obtained, the ease of administration, the absence of radiation sickness and toxic symptoms, the concentrated effect of the irradiation on the cells of the bone marrow, together with the fact that radioactivity disappears gradually and dosage can be adequately controlled indicate that this method of treatment is superior to other methods employed in the past. However, leukopenia, thrombocytopenia and anemia may be produced and adequate observation is essential to prevent irreversible damage to the bone marrow.

It is good to know that an adequate supply of radioactive phosphorus will be available when the necessities of war have passed. It will then be possible to determine accurately the proper frequency of administration and effective dosage. Although it has been demonstrated that intravenous administration is preferable for various reasons, yet because of the desirability of oral administration from a practical standpoint, this method of administration should be carefully evaluated.

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#### RECENT STUDIES ON YELLOW BONE MARROW EXTRACTS

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IN 1933 C. W. Watkins<sup>4</sup> of the Mayo Clinic announced that beneficial results could be obtained in the treatment of agranulocytosis by the

oral administration of strained yellow bone marrow. This was confirmed by M. J. Flipse,<sup>1</sup> and later C. M. Marberg and H. O. Wiles<sup>3</sup> demonstrated that the active leukopoietic principle was present in the unsaponifiable fraction of yellow bone marrow. This fraction was employed in the work to be described. The purpose of this investigation was to develop a suitable assay method which would be specific for yellow bone marrow concentrate.

**Materials and Methods.** The rabbit was chosen as the test animal because of greater constancy in his total and differential white blood cell counts than in those of guinea pigs and rats in our colonies. The average white blood cell count was 11,200 (range, 7900 to 13,300). The average percentage of segmented neutrophils was 31% (range, 27 to 42%). In order to determine the daily and hourly fluctuation of the total white and differential blood cell counts, estimations were made at 2 hour intervals for 3 consecutive days prior to the actual assay. None of the animals studied exhibited marked fluctuation.

It was discovered that the intramuscular injection of small quantities of the unsaponifiable fraction of yellow bone marrow produced a sharp increase in the number of segmented neutrophils in the circulating blood. Control experiments were conducted using comparable doses of olive oil, cod liver oil, carotene in oil and parenteral liver extracts. Each substance effected increases comparable to those observed after yellow bone marrow administration. The effect, therefore, was non-specific.

It was apparent from these results that it might be necessary to simulate human agranulocytosis in experimental animals in order to provide a test object. Several of the techniques described in the literature were investigated. One of the most convenient was a modification of a procedure for poisoning rabbits with benzene described by Kracke.<sup>2</sup>

Each of 10 rabbits was given 1 cc. daily subcutaneous injections of a solution consisting of 1 part benzene to 1 part olive oil for 30 consecutive days. A mild granulocytic leukocytosis rather than a leukopenia resulted. It was found, however, that by increasing the dosage to 2 daily subcutaneous injections of a solution containing 5 parts of benzene to 1 part of olive oil, it was possible to deplete 80% of the rabbits to a level of 2500 white blood cells per c.mm. in an average of 10 days.

**Blood Picture of Benzene Treated Rabbits.** A primary rise in the total white blood cell count of 2000 to 5000 cells per c.mm. was observed during the first few days of benzene administration. This increase was followed by a cyclic fluctuation in periods of 2 to 4 days. The peaks became progressively lower until total leukocyte counts of 2500 cells per c.mm. or less persisted.

**Myeloid Cells.** Wright's staining method was used. There was an initial rise in the absolute number and the relative percentage of myeloid cells. This was followed by a cyclic fluctuation which showed a progressive shift to the left in Schilling's index. Toxic characteristics, consisting of large forms with pale staining, irregular shaped nuclei and large amounts of "muddy," bluish staining cytoplasm, were noticed after 5 or 6 days of benzene administration. The picture became progressively worse until a relative myeloid percentage of 10% or less was found.

**Lymphoid Cells.** Here again an initial increase in the absolute number of lymphocytes occurred during the first few days of benzene administration, followed by a cyclic fluctuation in which the relative

percentage was increased after each rise. Large cells characterized by considerable amounts of bluish cytoplasm and azure cytoplasmic granules were observed.

*Monocytes.* A slight increase in monocytes was found in the majority of rabbits under test.

*Erythrocytes.* A mild hyperchromic, macrocytic type of anemia became evident after 10 days of benzene therapy. Rabbits with prolonged depletion times, however, exhibited a more severe idiopathic-hypochromic type. This was, in part at least, due to a general nutritional deficiency since these rabbits usually refused food and lost considerable weight.

*Thrombocytes.* Thrombocytes were reduced from a starting average of 280,000 to 160,000 per c.mm.

*Coagulation Time.* The average coagulation time of the blood was increased from 4 to 8 minutes.

*Body Temperature.* The body temperature of rabbits receiving benzene was elevated from 103° F. to an average of 106° F.

*Physical Appearance.* All the test animals displayed symptoms characterized by weakness, distress, incoördination and dry coats. The average loss of weight during the depletion period was 200 gm. per rabbit.

*Bone Marrow (Femur).* Bone marrow samples were taken aseptically before and after benzene treatment, and at the end of the test. The rabbits were given a light ether anesthesia and a 1 inch horizontal incision made along the upper one-third of the femur. A small puncture was then made into the bone marrow cavity with an electric dental drill and a desired amount of bone marrow removed by aspiration. Smears were made by the "imprint" method and stained with Wright's stain. The smears were examined and designated as aplastic or hyperplastic as compared to reference photomicrographs shown below.

Photomicrographs were taken from preparations selected as being representative of the various phases in depletion and repletion as determined in previous experiments.

*Response to Therapy of Benzene Depleted Rabbits.* A series of experiments were carried out on benzene depleted rabbits to determine the leukopoietic value of yellow bone marrow extracts compared with that of other materials tested on normal rabbits. The results are shown in Table 1. Erythrocytes and hemoglobin were not affected significantly and are not shown here.

The rabbits used in these experiments were male albino rabbits weighing approximately 2.5 kg. These rabbits were depleted by means of twice daily subcutaneous injection of a 5:1 benzene olive oil solution. Benzene was discontinued when leukocyte counts of 2500 cells per c.mm. persisted for 2 consecutive days and daily intramuscular injections of test material begun. Maximum response was obtained from a daily dose of material representing 21 mg. of the unsaponifiable fraction of yellow bone marrow. Smaller amounts gave inconsistent results.



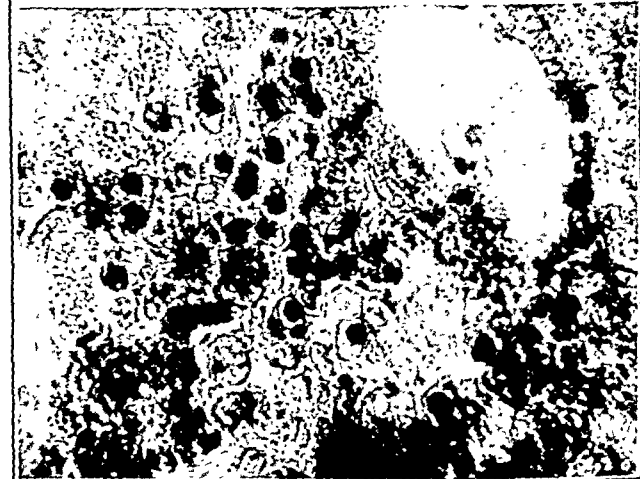


FIG. 1.—Normoplastic control, normal rabbit bone marrow (femur).



FIG. 2.—Aplastic control (femur), benzene treated, olive oil treated.

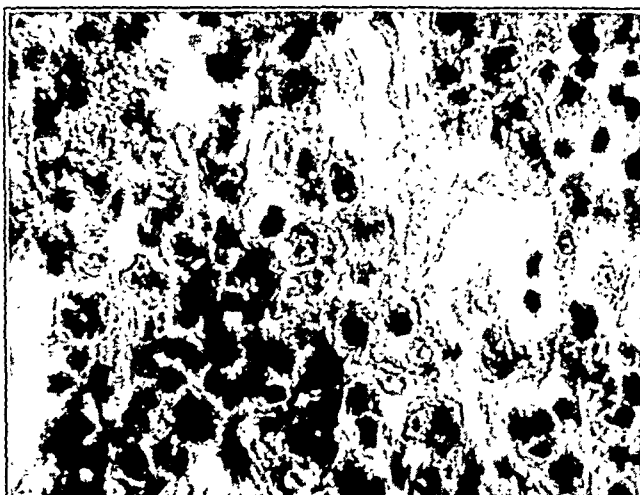


FIG. 3.—Hyperplastic control (femur), benzene depleted, yellow bone marrow treated.

TABLE 1.—LEUKOCYTE COUNTS IN DEPLETED RABBITS BEFORE AND AFTER TREATMENT

	GROUP A	GROUP B	GROUP C	GROUP D	GROUP E
Therapy (½ cc. daily for 14 days) . . .	Y.B.M. in olive oil	Olive oil	Cod liver oil	15 units parenteral liver	Carotene concentrate
Number of rabbits depleted . . . .	27	27	3	3	6
Total white cells per c.mm. at start of therapy	Mean 2,331 Stand. dev. 477 S. E. mean $\pm 93.6$	2,044 543 $\pm 106.7$	1,933 511 $\pm 361$	2,133 603 $\pm 426$	2,516 471 $\pm 208$
Total segmented neutrophils at start of therapy (per c.mm.)	Mean 378 Stand. dev. 492 S. E. mean $\pm 96.6$	249 274 $\pm 53.8$	228 658 $\pm 465$	410 154 $\pm 108.9$	278 195 $\pm 86.2$
Number of rabbits surviving therapy .	26	22	3	2	5
Average weight change during therapy .	+192	+20	+220	+57	-10
Condition of bone marrow at end of therapy . . . . .	Hyperplastic	Aplastic	Aplastic	Aplastic	Aplastic
Total white cells per c.mm. at end of therapy	Mean 11,403 Stand. dev. 3,868 S. E. mean $\pm 773$	3,376 1,933 $\pm 422$	3,017 451 $\pm 319$	2,550 636 $\pm 636$	5,240 1,694 $\pm 847$
Total segmented neutrophils per c.mm. at end of therapy	Mean 4,473 Stand. dev. 1,863 S. E. mean $\pm 332.6$	690 855 $\pm 186.5$	327 319 $\pm 225$	192 153 $\pm 153$	723 638 $\pm 319$

**Summary.** Normal, untreated, albino rabbits were given comparable amounts of 15 unit liver extract (Armour), cod liver oil, whole milk, concentrated carotene solutions and extracts of yellow bone marrow by intramuscular injection. There was a comparable increase in the absolute number and relative percentage of circulating granulocytes, within 4 to 6 hours after administration of test material. The response in each case was similar and therefore non-specific.

Following a modification of the procedure described by Kracke<sup>2</sup> of giving twice daily 1 cc. subcutaneous doses of a solution consisting of 5 parts of benzene to 1 part of olive oil, approximately 80% of the rabbits developed a granulocytopenia in an average period of 10 days.

Rabbits which were benzene poisoned in this manner and given daily intramuscular doses of Armour's 15 unit liver extract, cod liver oil, whole milk, or concentrated carotene solutions for 14 consecutive days showed no evidence of either physical, leukocytic or clinical response. Similarly poisoned rabbits, however, when given comparable doses of yellow bone marrow extracts showed immediate response and complete physical, leukocytic and clinical recovery by the 14th day.

**Conclusion.** Extracts of yellow bone marrow, in contrast to all other materials tested, contain a specific substance or substances which stimulate leukopoiesis in benzene poisoned rabbits.

The authors are indebted to D. V. Hall for the statistical treatment of the results obtained.

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## ABDOMINAL CRISES IN UNCOMPLICATED SICKLE CELL ANEMIA

A CLINICO-PATHOLOGIC STUDY OF 11 CASES WITH A SUGGESTED  
EXPLANATION OF THEIR CAUSE

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THE cause of the so-called abdominal crises in sickle cell anemia is unknown. There is also a general impression that death as a result of uncomplicated sickle cell anemia is relatively rare. Steinberg<sup>1</sup> in a review of sickle cell anemia states "The prevailing conception is that sickle cell anemia *per se* is not fatal." Wintrobe<sup>2</sup> leaves the same general impression in discussing the complications and prognosis in sickle cell anemia. Some of the cases of sickle cell anemia in this institution reveal a different picture and a clinico-pathologic study of abdominal crises in uncomplicated sickle cell anemia with a physiologic explanation of the crises and cause of death is presented.

**Material.** The autopsy protocols of this institution have been studied and the racial incidence of sickle cell anemia in this area is given in another report.<sup>3</sup> In these protocols there are 24 cases in which a diagnosis of sickle cell anemia was made following postmortem examination. Of these, 13 cases were accompanied by other conditions which make it highly probable that sickle cell anemia *per se* was not the important factor in their deaths. The pertinent autopsy findings and causes of death in these 13 cases are given in Table 1. A critical review of these cases raises considerable doubt regarding the presence of sickle cell anemia in Cases 10, 11, 12 and 13; they seem to fit more clearly into the group of sickle cell patients dying from varied causes with no clinical or autopsy evidence of sickle cell anemia. In the remaining 9 of these 13 cases there was clinical and autopsy evidence of sickle cell anemia but other conditions were present at autopsy which are more probably the actual causes of death.

The material forming the basis of this report consists of the remaining 11 cases of active sickle cell anemia presenting the picture of abdominal crisis in sickle cell anemia with no complicating chronic illnesses.

**Case Reports.** In this group of cases that represent abdominal crises in uncomplicated sickle cell anemia there is a striking clinical and autopsy picture which will be given in some detail. All these cases were negative for malaria parasites on both thin and thick smears where the patient was admitted to the hospital and no malaria parasites were found in the blood and tissue smears taken in all cases at autopsy. Blood sera taken during life and in all autopsy specimens were negative to both Kahn and Wassermann examinations. Autopsies were performed on all 11 cases.

**CASE 1.** A Panamanian female child, aged 8 months, was admitted Aug. 18, 1939, because of vomiting, weight loss, and grunting respirations of intermittent character during the past 2 weeks. There had been no previous illnesses. Physical examination revealed a temperature of 100° F. The baby was dehydrated and emaciated, with dry hot skin. The cervical lymph nodes were slightly enlarged but not soft or tender. No changes were demonstrated in the heart. There were a few coarse râles at the bases of both lungs. The

abdomen was tense but not rigid and the liver and spleen were not palpable. Admission hemogram was: hemoglobin 25% (Sahli), erythrocytes 2,130,000 per c.mm., and leukocytes 22,800 per c.mm. Differential was: neutrophils 54 and lymphocytes 46. There were 6 nucleated erythrocytes encountered in counting 100 leukocytes and the erythrocytes showed 5% sickled forms on the smear. Urinalysis was negative.

TABLE 1.—AUTOPSY FINDINGS IN 13 OTHER CASES DIAGNOSED AS SICKLE CELL ANEMIA WITH DEATH RESULTING FROM OTHER CONDITIONS

Case No. . . . .	1	2	3	4	5	6	7	8	9	10	11	12	13
Race* . . . . .	BWI	Pan	BWI	BWI	Pan	BWI	Pan	BWI	BWI	BWI	BWI	Pan	Pan
Sex . . . . .	M	M	F	M	M	F	F	F	F	F	F	M	M
Age (yrs.) . . . . .	5/12	1	1½	3	7	11	22	22	23	23	36	43	51
Leg ulcers, healed . . . . .	..	..	..	+	..	..	+	+	..	..	+	+	..
Peripheral edema . . . . .	+	..	..	..	..	..	+	..	..	..	+	+	..
Marasmus . . . . .	+	+	..	..	..	+	..	..	..	..	..	..	+
Jaundice . . . . .	+	..	..	..	..	+	..	..	..	..	..	..	+
Rickets . . . . .	..	..	..	+	..	..	..	..	..	..	..	..	..
Mastoiditis, purulent . . . . .	..	..	..	..	+	..	..	..	..	..	..	..	..
Purulent meningitis . . . . .	..	..	..	..	+	..	..	..	..	..	..	..	..
Brain:													
Edema . . . . .	..	..	..	..	..	..	..	..	..	+	..	+	+
Abscess . . . . .	..	..	..	..	..	+	..	..	..	..	..	+	+
Arteriosclerosis . . . . .	..	..	..	..	..	..	..	..	..	..	..	+	+
Lung:													
Chronic passive con. . . . .	..	..	..	+	..	+	+	..	+	..	+	+	+
Bronchopneumonia . . . . .	+	+	..	+	+	+	..	..	..	..	..	+	+
Infarction . . . . .	..	..	..	..	..	..	+	..	..	..	..	..	..
Vessel thrombosis . . . . .	..	..	..	..	..	..	+	..	..	..	..	..	..
Pleural effusion . . . . .	+	+	..	..	..	..	..	..	..	+	+	+	+
Heart:													
Hypertrophy . . . . .	..	..	..	..	..	+	+	..	..	..	+	..	+
Endocarditis . . . . .	..	..	..	..	..	..	+	..	..	..	..	..	..
Pericardial effusion . . . . .	..	+	..	..	..	..	..	..	..	..	+	..	..
Ascites . . . . .	..	..	..	..	..	+	+	..	..	+	+	+	+
Liver:													
Chr. pass. congest. . . . .	+	..	..	..	..	+	+	..	..	..	+	+	+
Chr. hepatitis . . . . .	..	..	+	..	..	..	..	+	+	..	+	+	+
Cirrhosis, luetic . . . . .	+	..	..	..	..	..	..	..	..	..	..	..	..
Glomerulonephritis:													
Acute . . . . .	..	..	..	..	..	..	..	..	+	..	..	..	..
Chronic . . . . .	..	..	..	..	+	..	+	..	..	..	+	..	..
Interstitial nephritis . . . . .	..	..	+	..	..	..	..	..	..	..	..	..	+
Nephrosis . . . . .	..	..	..	..	..	..	..	..	..	..	..	+	..
Pyelitis . . . . .	..	..	..	..	..	..	..	..	..	+	..	..	..
Pyosalpingitis . . . . .	..	..	..	..	..	..	..	..	+	..	..	..	..
Cellulitis of arms and legs . . . . .	..	..	+	..	..	..	..	..	..	..	..	..	+
Postpartum septicemia . . . . .	..	..	..	..	..	..	..	..	..	+	..	..	..
Septicemia . . . . .	..	..	..	..	..	+	..	..	..	..	..	..	+
Liver weight (gm.) . . . . .	155	265	160	535	800	620	1300	890	2100	1200	1090	1630	2920
Spleen weight (gm.) . . . . .	20	20	15	50	150	5	190	140	20	420	185	505	700
Cause of death . . . . .	Congenital lues	Marasmus and bronchopneumonia	Cellulitis of leg with toxic hepatitis	Rickets	Mastoiditis with meningitis	Septicemia with brain abscess	Chronic glomerulonephritis, mural endocarditis	Pyosalpingitis, death during ether anesthesia	Postpartum septicemia	Congenital mobile colon with torsion and gangrene	Chronic glomerulonephritis	Nephrosis	Acute toxic anemia with septicemia

\* BWI, British West Indian; Pan, Panamanian.

*Clinical Course.* The child was quite weak and vomited every other feeding. Hartman's solution was given frequently. The baby gained weight for 5 days and then gradually began to lose, seeming to be a feeding problem. At 4 P.M. on August 31 she became very restless, vomited profusely, and the temperature dropped to 97.4° F., with a rapid pulse and respiratory rate. At 2 A.M., September 1, she was grunting, cyanotic, and the peripheral circulation was

collapsed. She was given supportive treatment (no transfusions) but expired at 3:46 P.M., September 1, approximately 12 hours after the onset of the acute abdominal symptoms.

**CASE 2.** A Panamanian-Costa Rican male, aged 11 months, was admitted May 30, 1944 at 9:15 A.M., with the following history obtained from the mother. About 2 A.M. the day of admission the baby started to scream, then groan and grunt as though he had pain in his stomach. The eyes rolled about and he had minor rigid moments but no convulsions. His mother noted that the hands were swollen. The baby had passed 2 normal stools that morning, vomited twice, and refused both breast and bottle feedings. There had been no previous illnesses. Physical examination revealed a moribund, dehydrated baby who was breathing irregularly and rolling its eyes as though unconscious. There was no spasticity of the body. It was noted that the hands and feet were edematous, that the mucous membranes were pale, and there were a few petechiae over the legs. The baby expired during the examination at 9:55 A.M., 40 minutes after admission and approximately 8 hours after the onset of acute symptoms.

**CASE 3.** A Panamanian girl, aged 19 months, was dead upon arrival of a physician at her home July 7, 1942; death was said to have occurred approximately 10 minutes before. The history as obtained from the child's family was that she developed "a cold" the morning of July 5. In the afternoon she was listless, moaned occasionally, and had severe nausea and vomiting. No blood was seen in the vomitus. The past history revealed a similar episode approximately 2 months before, lasting 1 day, and the child apparently recovered without medical care.

**CASE 4.** A British West Indian female, aged 2 years 3 months, was admitted March 19, 1930, with fever, jaundice, and pain in the right arm. The fever and pain in the arm began the day before admission; jaundice had been present for 1 week. Past history revealed no illness and apparently normal development. Physical examination revealed temperature 101° F., pulse 140, and respirations 30 per minute. The heart and lungs were negative. The abdomen was distended and tympanitic with the liver palpably enlarged. The spleen could not be palpated. The lower two-thirds of the right arm showed some swelling and tenderness but no localization or fluctuation. Roentgenogram revealed slight periostitis on the inner aspect of the lower two-thirds of the humerus. This cleared up spontaneously in the following 10 days. Admission urinalysis and subsequent ones were within normal limits. No blood chemical studies were recorded. Admission hemogram was: hemoglobin 60% (Sahli), erythrocytes 3,300,000, leukocytes 23,100 per c.mm. (neutrophils 68, eosinophils 2, lymphocytes 30%). There were 2 nucleated erythrocytes encountered in counting 100 leukocytes and approximately 5% of the erythrocytes were sickled.

*Clinical Course.* The patient's jaundice did not increase clinically. The temperature remained around 99° F. and the patient had no complaints until April 17, 1930, when she suddenly complained of severe abdominal pain, with the onset of nausea and vomiting. Hemograms in the interim had been similar to the one on admission. Hemogram taken after the onset of abdominal pain was: hemoglobin 55% (Sahli), erythrocytes 2,460,000; leukocytes 15,000 per c.mm. (neutrophils 52, lymphocytes 48%). Ten nucleated erythrocytes were encountered, and approximately 15% of the erythrocytes on the smear were sickled. The evening of April 17 the temperature was 103° F., with pulse 150, and respirations 40 per minute. The next day vomiting of dark bile-colored fluid and intense abdominal pain continued. The temperature was 104° F. On April 18 the vomitus became blood-tinged; the abdomen was firm and tympanitic. The temperature was 106° F., with pulse 160, thready, and respirations 60 per minute. Shock and collapse were apparent and the patient was irrational and hyperexcitable. Hemogram April 19 was: hemoglobin 65% (Sahli), erythrocytes 2,840,000 and leukocytes 42,900 per c.mm. (neutrophils 75, lymphocytes 25%). Fifteen nucleated erythrocytes were encountered, and approximately 25% of the erythrocytes were sickled.

The patient expired in typical circulatory collapse and shock at noon April 19, 1930, approximately 48 hours after the onset of the acute abdominal pain.

CASE 5. A Honduran-Nicaraguan male, aged 3 years 7 months, was admitted the last time May 21, 1944, at 4:30 P.M. with complaints of vomiting and convulsions. The child's illness really began March 14, 1944, with the sudden onset of nausea, vomiting, and lethargy followed in 3 hours by a convulsion. The convulsion was characterized by opisthotonos, clenching of the hands, and rolling of the eyes. Following the convulsions, coma would last about 4 hours and then there was marked disorientation until the next convulsion. The convulsions occurred about every 8 hours, did not increase in severity, and lasted about 45 seconds. They were not precipitated by light, sound, or motion. The past history at this time was negative and there had been no similar attacks. Physical examination at this time revealed a well-developed, well-nourished, anemic, disoriented child with temperature of 102.5° F.; no pulse or respiratory rates were recorded. The skin was hot and dry and there was moderate peripheral edema present. The superficial lymph nodes were just palpable. The heart was not enlarged, there were no murmurs, and the rate was rapid. The lungs were clear. The abdomen was soft and no masses were palpable. The pupils were equal, round, and reacted sluggishly to light. Neurologic examination revealed bilateral hyperactive deep reflexes which were equal in the upper and lower extremities. The abdominal reflex was hypoactive on the left side. Babinski reflexes were negative. Admission hemogram was: hemoglobin 26% (Haden-Hausser), erythrocytes 2,060,000 and leukocytes 44,700 per c.mm. (neutrophils 64, lymphocytes 36%). Eight nucleated erythrocytes were encountered but no notation was made of sickled forms. Urinalysis was negative. Spinal fluid cell counts on 3 successive days following admission were 3, 3 and 5 cells per c.mm.; smears and cultures were negative and no pellicle formation was present. Blood and stool cultures were repeatedly negative.

*Clinical Course.* The temperature ranged in the vicinity of 105° F. for 3 days following admission in spite of sulfadiazine therapy. On March 18 a transfusion of 300 cc. of citrated blood was given with no reaction and the temperature leveled off and returned to normal in 2 days. The convulsions likewise stopped; there was one the morning following the transfusion. The patient was somewhat disoriented for 6 days following the last convulsion and on March 27 seemed to be mentally clear. At this time hemogram was: hemoglobin 52% (Haden-Hausser), erythrocytes 3,120,000 and leukocytes 9500 per c.mm. Differential count was normal and no nucleated erythrocytes or sickled forms were recorded. Neurologic consultation at this time showed no residual involvement and no diagnosis was made. Patient was kept in the hospital for 3 weeks with no recurrence of signs or symptoms and then discharged to the Pediatric Clinic.

Following discharge the child was apparently well and had been seen in the clinic. On May 19, 1944, he complained of abdominal distress, started vomiting, and refused food. He was taken to the Pediatric Clinic on May 21, and at 3 P.M., while there, had a convulsion identical with those of the previous admission. He was admitted to the hospital at 4 P.M. the same day. His temperature was 99° F.; no pulse or respiratory rates were recorded. No physical examination was done due to the convulsions which were severe, lasted approximately 5 minutes, and occurred about every 4 hours. Admission hemogram was: hemoglobin 25% (Tallqvist), erythrocytes 1,900,000 and leukocytes 47,500 per c.mm. (neutrophils 40, eosinophils 5, lymphocytes 55%). Five nucleated erythrocytes were encountered but no sickled forms were mentioned. The clinical course was downhill with repeated convulsions. The day following admission he developed râles in both bases, and the temperature was 105° F., with pulse 170 and respirations 56 per minute. The last convulsion was at 5:30 P.M., May 22, and the patient was comatose following this until death, May 23, 1944, at 1:30 A.M., approximately 33 hours after admission to the hospital.

CASE 6. A British West Indian-Panamanian male, aged 4 years 1 month, was admitted April 4, 1935, at 7:10 A.M. with complaints of stiffness of neck and stupor. The boy had seemed well until the night before admission when he cried, had stiffness of the extremities, and would not respond to questions. The past medical history revealed 2 single convulsive seizures similar to this attack in the past year; no further information concerning these could be obtained. The statement was made that he had never been a strong child. Physical examination revealed a seriously ill, comatose, poorly developed child with temperature of 97.6° F., pulse 158, and respiratory rate 56 per minute. There was a small ulcer along the lateral malleolus of the left leg. The mucous membranes and conjunctivæ were pale. There was a faint systolic murmur at the apex which was not transmitted. There were coarse râles at the bases of both lungs but no consolidation was present. The abdomen was soft; the spleen was enlarged to the umbilicus; the liver was not palpably enlarged. At the time of examination there was no rigidity of the neck or extremities. The knee jerks were exaggerated and there was bilateral ankle clonus. Bicep, abdominal, and plantar reflexes could not be obtained. Admission hemogram was: hemoglobin 15% (Tallqvist), erythrocytes 590,000 and leukocytes 83,600 per c.mm. (neutrophils 46, lymphocytes 50, monocytes 4%). Many nucleated erythrocytes and sickled forms were seen in the smear. No urine was obtained. Spinal fluid was clear, under no increased pressure, and no pellicle formed on standing; smears and cultures were negative. Icterus index was 10 units. The patient expired at 10:10 A.M., April 4, 1935, 3 hours after admission.

CASE 7. A British West Indian female, aged 4 years 7 months, was admitted September 10, 1933, at 11:30 A.M. She was brought to the hospital by a family friend who left immediately. The child expired 10 minutes later and was not seen by a physician. The father was located and gave the following information. The child had developed fever the previous afternoon and in the evening cried with pain in the abdomen. The morning of admission she was restless, irrational, and vomited several times. The family friend called a physician who immediately upon seeing the child ordered her to be taken to the hospital.

The past medical history revealed an admission to the hospital March 17, 1932, with complaints of fever, vomiting, abdominal pain and rigidity of 1 day's duration. There had been no prior episodes similar to this and no other illnesses. Physical examination on the previous admission showed temperature of 102° F., pulse 120, and respiratory rate 34 per minute. There was a low grade jaundice present. The mucosal surfaces were pale. The heart and lungs were normal. The abdomen was rigid, tender and distended. The liver was enlarged, extending 3 cm. below the costal border. The spleen extended to the level of the umbilicus and was firm and nodular. Admission hemogram was: hemoglobin 40% (Sahli); erythrocytes 1,700,000; leukocytes 16,000 per c.mm. (neutrophils 35, eosinophils 5, lymphocytes 60%). Many nucleated and sickled forms of erythrocytes were seen on the smear. Urinalyses were positive for urobilin. The clinical course was good with gradual return to normal of the temperature, pulse and respirations. The leukocytosis disappeared in 3 days. The child was given iron and tonics during the two week hospitalization and was discharged by request on March 21, 1932. The discharge hemogram on the earlier hospital stay was: hemoglobin 30% (Sahli), erythrocytes 1,300,000 and leukocytes 7500 per c.mm. The patient had not been seen in the interim before the last admission.

CASE 8. A British West Indian female, aged 5 years 3 months, was admitted January 14, 1931, at 2:55 A.M., with pain in the abdomen, nausea, vomiting and fever. The abdominal pain began on January 11 and vomiting started the next day; fever was first noticed then. Her past history was non-contributory other than the statement "she was subject to colds." Physical examination revealed temperature 98° F., pulse 150, and respiratory rate 64 per minute. The notation was made that the child was obviously in shock and having severe pain. There was marked pallor of the mucous membranes.

The heart was rapid but no murmurs were heard; the pulse was weak. The lungs were clear. The abdomen was distended and rigid, especially in the upper portion. The liver was palpable and firm with the lower edge extending to the umbilicus. The spleen was palpable 2 inches below the anterior costal margin. The superficial lymph nodes were palpably enlarged but not tender.

*Clinical Course.* An emergency blood count revealed leukocytes 63,000 per c.mm. (neutrophils 42, lymphocytes 48, undetermined cells 10%). There were 30 nucleated erythrocytes encountered and 15% of the erythrocytes were sickled. No hemoglobin or erythrocyte determinations were done and no urine was voided. The patient failed rapidly, became pulseless at 6:30 A.M., and expired at 7 A.M. the same day, 4 hours after admission.

CASE 9. A British West Indian female, aged 9 years 9 months, was found dead at her home upon the arrival of an ambulance to take her to the hospital on December 22, 1940, at 3:30 P.M. The following history was obtained from the parents. The afternoon of December 18 she complained of pain in the upper abdomen which would last for 2 to 3 hours and then disappear for periods of 4 to 5 hours. On December 20 she was very listless, had intermittent pain in the abdomen and a fever. At noon December 22 she was taken to a doctor who told the mother the girl was very sick and sent her home to go to the hospital. On reaching her house she lay down for approximately 15 minutes, had a general convulsion, and died immediately following the convulsion at approximately 3:30 P.M., Dec. 22, 1940, 4 days after the onset of symptoms.

The past medical history revealed an admission to the hospital in December, 1931, for lobar pneumonia; there were no other illnesses. Physical examination at that time was negative beyond a marked anemia and the typical findings of lobar pneumonia. Hemogram was: hemoglobin 29% (Sahli), erythrocytes 1,590,000 and leukocytes 30,000 per c.mm. (neutrophils 88, lymphocytes 11, monocytes 1%). No notation of sickled erythrocytes was made. The patient was taken home by signing a release 5 days after admission and had not been seen in the intervening 9 years.

CASE 10. A British West Indian female, aged 11 years 6 months, was admitted Feb. 17, 1931, at 9 A.M. with complaints of fever, malaise, pain in abdomen, nausea and vomiting. The illness began February 14 with nausea and vomiting, fever, but no chills. This was accompanied by pain in the bones around the knees and in the upper abdomen. The pain had become progressively more severe. On February 16 she had a dose of epsom salts in the morning. That evening the urine was smoky and scant. Past history showed no prior hospitalizations and general good health beyond occasional head colds. Physical examination revealed a normally developed, dehydrated female in severe shock. The skin was hot and dry and there was marked pallor of the mucous membranes. The scleras were jaundiced. The heart and lungs were negative. Temperature was 102° F., pulse 120, and the respiratory rate was 30 per minute. The abdomen was rigid, distended and painful. The liver was enlarged, painful and extended 6 cm. below the costal border. The spleen was not palpable. There was vague tenderness on deep percussion in the costovertebral angles. Admission hemogram was: hemoglobin 45% (Sahli), erythrocytes 1,810,000 and leukocytes 49,400 per c.mm. (neutrophils 52, eosinophils 1, lymphocytes 40, monocytes 7%). There were 116 nucleated erythrocytes encountered in counting 100 leukocytes and the erythrocytes showed a high percentage of sickled forms. Urinalysis was clear, negative for blood, and showed 1+ albumin. Blood culture taken on admission was negative. Icterus index was 39 units.

*Clinical Course.* The patient failed rapidly, becoming irrational. The temperature went to 104° F. and remained at that level until death. Pulse ranged around 150 and was weak and thread-like. Respirations became more labored and shallow, and reached 64 per minute. She gradually developed râles and pulmonary edema, expiring at 2 P.M., Feb. 18, 1931, 29 hours after admission.

CASE 11. A Panamanian female, aged 18 years 10 months, was admitted Dec. 11, 1931, at 11:20 A.M. in an irrational and acutely ill condition. Accord-



ing to an accompanying friend the patient was taken suddenly with pain in the adomen, fever, nausea and vomiting the afternoon of December 9. The vomitus became blood-flecked the next day and the patient developed some diarrhea. The morning of admission she was very ill and acted "queer" at times, finally becoming irrational just before admission. Her past history was non-contributory and there had been no similar episodes. Physical examination revealed temperature 103° F., pulse 140, and respiratory rate 48 per minute. She was irrational, apprehensive, and acutely ill. The skin was dry and hot; the mucosal surfaces were pale and anemic. The scleras were jaundiced; the pupils were widely dilated and reacted sluggishly to light.

TABLE 2.—GROSS AUTOPSY FINDINGS IN 11 CASES OF ABDOMINAL CRISIS IN SICKLE CELL ANEMIA

Case No. . . . .	1	2	3	4	5	6	7	8	9	10	11
Age in years . . . . .	0.66	0.9	1.5	2.25	3.65	4.1	4.55	5.25	9.7	11.5	18.7
Jaundice . . . . .	..	+	..	+	+	..	+	..	+	+	+
Peripheral edema . . . . .	+	..	+	..	+	+	..	+	..	+	..
Leg ulcers, healed . . . . .	..	..	..	..	+	..	..	+	+	..	+
Leg ulcers, active . . . . .	..	..	..	..	..	+	+	+	..	..	..
Palpable lymph nodes . . . . .	..	+	+	+	+	+	..	..	+	..	..
Brain:											
Edema . . . . .	..	+	+	+	+	+	+	+	+	+	..
Congestion, marked . . . . .	+	+	+	+	+	+	+	+	+	+	..
Petechial hemorrhages . . . . .	..	..	..	..	+	..	..	+	..	+	..
Heart:											
Fatty changes . . . . .	+	..	..	+	+	+	+	+	..	+	+
Hypertrophy . . . . .	..	..	..	+	+	+	+	+	+	+	+
Pleural effusion . . . . .	..	+	+	..	+	+	+	+	..	..	..
Lungs:											
Congestion . . . . .	+	+	..	+	+	..	+	..	+	+	+
Edema . . . . .	+	+	..	+	+	..	+	..	+	+	+
Ascites . . . . .	+	+	..	..	..	..	..	+	..	..	..
Liver:											
Fatty changes . . . . .	+	+	..	+	+	+	+	+	..	+	+
Congestion . . . . .	+	+	+	+	+	+	+	+	+	+	+
Petechial hemorrhages . . . . .	..	..	..	..	+	+	+	..	..	+	..
Gallstones . . . . .	..	..	..	..	..	..	..	..	..	..	+
Spleen:											
Perisplenitis . . . . .	..	..	..	+	..	+	..	+	+	+	+
Congestion . . . . .	+	+	+	+	+	+	+	+	+	+	+
Fibrosis . . . . .	+	+	+	+	+	+	+	+	+	+	+
Infarction . . . . .	..	..	..	..	..	..	..	..	..	+	..
Calcium . . . . .	..	..	..	..	..	+	..	..	..	..	..
Kidneys:											
Swollen . . . . .	..	+	+	+	+	+	+	+	..	+	..
Scarring . . . . .	..	..	..	..	..	..	+	..	..	+	..
Gastro-intestinal tract:											
Dilated, atonic . . . . .	+	..	..	..	+	..	+	+	..	..	..
Congested mucosa . . . . .	+	+	+	..	+	..	+	+	+	..	..
Petechial hemorrhages . . . . .	..	..	..	..	+	..	..	+	+	..	..
Lymph nodes, internal:											
Enlarged . . . . .	+	+	+	+	+	+	+	+	+	+	+
Soft . . . . .	+	+	+	+	+	+	+	+	+	+	+
Hemorrhagic . . . . .	..	..	..	..	+	..	..	..	..	..	..
Bone marrow:											
Hyperplastic . . . . .	..	+	..	+	+	+	+	+	+	+	+
Soft . . . . .	..	+	..	..	+	+	..	..	..	..	..
Not mentioned . . . . .	+	..	+	..	..	..	..	..	..	..	..

The heart sounds were faint, rapid, and there was a weak systolic murmur heard over the apex. The breathing was stertorous and no alveolar sounds could be heard. The abdomen was rigid, distended, and obviously painful on manipulation, especially in the epigastrium. The liver could not be palpated due to the rigidity. The spleen was palpable 3 cm. below the lateral costal border. Hemogram on admission was: hemoglobin 11% (Sabli), erythrocytes 690,000 and leukocytes 30,300 per c.mm. (neutrophils 65, lymphocytes 27, normoblast 8%). No mention was made of sickled erythrocytes. Urinalysis was smoky, positive for hyaline casts and pus cells, and showed 1+ albumin. Icterus index was 38 units,

*Clinical Course.* The patient failed rapidly. Note was made that attempts to obtain blood specimens for chemistry were unsuccessful due to the complete venous collapse. She expired at 2:30 p.m., Dec. 11, 1931, 3½ hours after entering the hospital.

*Autopsy Reports.* The autopsy data in the 11 cases are presented in tabular form for the most part, the case numbers corresponding to the cases above. The gross autopsy findings are given in Table 2, the organ weights in Table 3, and the autopsy blood chemistry determinations are presented in Table 4. The microscopic findings are presented in Table 5. The autopsy findings that are due to the sickle cell anemia are discussed in more detail where they vary from other reports and because of the uncomplicated pictures presented in such an early age group.

TABLE 3.—NORMAL\* AND AUTOPSY ORGAN WEIGHTS IN 11 CASES OF ABDOMINAL CRISIS IN SICKLE CELL ANEMIA

Case No.	1	2	3	4	5	6	7	8	9	10	11
Sex	F	M	F	F	M	M	F	F	F	F	F
Age in years	0.66	0.9	1.5	2.25	3.65	4.1	4.55	5.25	9.7	11.5	18.7
Body weight (pounds)	8.5	9	16	22	37	28.5	36	40	57	82	101
Body length (inches)	24.5	26	30	33	38	..	42	42	57	59.5	59
<b>Brain:</b>											
Normal weight (gm.)	714	825	1042	1064	1165	1195	1200	1239	1280	1335	1350
Actual weight (gm.)	555	620	850	930	1300	1125	1210	1150	1365	1245	1150
<b>Heart:</b>											
Normal weight (gm.)	37	40	52	56	66	74	80	85	116	124	290
Actual weight (gm.)	35	30	50	80	100	100	132	125	215	275	300
<b>Right lung:</b>											
Normal weight (gm.)	52	59	72	88	90	92	100	107	176	201	350
Actual weight (gm.)	35	40	80	90	200	100	210	160	255	340	245
<b>Left lung:</b>											
Normal weight (gm.)	45	53	65	76	85	89	95	104	160	190	340
Actual weight (gm.)	50	60	50	70	190	75	195	155	230	305	215
<b>Liver:</b>											
Normal weight (gm.)	259	277	345	394	470	523	560	596	825	936	1550
Actual weight (gm.)	175	225	335	650	650	530	635	610	1100	1755	1730
<b>Spleen:</b>											
Normal weight (gm.)	20	26	30	33	39	40	44	47	85	93	150
Actual weight (gm.)	40	25	140	65	200	325	460	150	25	90	1425
<b>Kidneys (combined):</b>											
Normal weight (gm.)	61	71	83	93	106	116	123	129	185	190	260
Actual weight (gm.)	45	60	80	85	140	120	130	150	245	320	220

\* Mostly from Coppoletta and Wolbach, Am. J. Path., 9, 55, 1933.

TABLE 4.—AUTOPSY BLOOD CHEMISTRY FINDINGS IN 11 CASES OF ABDOMINAL CRISIS IN SICKLE CELL ANEMIA. (Mgm. per 100 cc.)

Case No.	1	2	4	5	6	8	9	10
Non-protein nitrogen	76.8	36.5	94.4	83.2	42.7	129.0	208.2	64.8
Urea nitrogen	35.1	20.9	61.0	50.5	22.6	84.8	132.4	26.8
Creatinine	1.6	..	1.7	2.5	1.6	4.1	4.0	1.1

*Brain.* These cases showed extensive degenerative changes in the small capillaries and venules of the brain, particularly in the region of the cortex. There were perivascular fibrosis, edema, infiltration by inflammatory cells, hyaline changes, and occasionally thrombosis or conglutination. There was rather extensive pyramidal cell degeneration with proliferation of fibrous tissue and in 5 cases (ages 1.5, 3.65, 4.55, 9.7 and 18.7 years) there was marked corpora amylacea formation.

*Heart.* The hearts were hypertrophied as seen in Table 3. There were fatty changes, albuminous degeneration, and edema present, with 3 cases showing perivascular cell infiltrations and degenerative changes in the small vessel walls. Fragmentation of the myocardial fibers was a frequent finding. There were no valvular or endocardial lesions present.

*Lungs.* In the lungs there were no noteworthy changes of fibrosis or vascular sclerosis, although these have been described as producing cardiac hypertrophy in sickle cell anemia.

TABLE 5.—MICROSCOPIC AUTOPSY FINDINGS IN 11 CASES OF ABDOMINAL CRISIS IN SICKLE CELL ANEMIA

Case No.	1	2	3	4	5	6	7	8	9	10	11
Sex	F	M	F	F	M	M	F	F	F	F	F
Age in years	0.66	0.9	1.5	2.25	3.65	4.1	4.55	5.25	9.7	11.5	18.7
<b>Brain:</b>											
Edema	+	+	+	+	+	+	..	+	+	+	+
Vessel dilatation and engorgement	+	+	+	+	+	+	+	+	+	+	+
Conglutination	+	..	+	+	..	+	..	..	+	+	+
Thrombosis	..	..	..	..	..	..	..	..	..	..	+
Pericapillary fibrosis	+	+	..	..	+	+	..	..	+	..	+
Pericapillary cell infiltration	..	+	+	..	+	+	..	..	+	..	+
Hyaline vessel changes	..	+	+	..	+	..	+	..	+	..	+
Calcospherite formation	..	..	+	..	+	..	+	..	+	..	+
Endothelial cell swelling	..	+	+	+	+	+	..	..	+	..	+
Pyramidal cell degeneration	+	+	+	+	+	+	+	..	+	+	+
<b>Heart:</b>											
Fragmentation	..	..	+	+	+	+	+	+	+	+	+
Albuminous degeneration	+	+	+	+	+	+	+	+	..	+	+
Fatty changes	+	..	..	+	..	..	..	+	..	+	+
Edema	+	+	+	+	+	+	..	+	..	+	+
Cell infiltration	..	..	..	..	+	+	..	+	..	..	+
<b>Lungs:</b>											
Alveolar capillary congestion	+	+	+	+	+	+	+	+	+	..	+
Capillary hemorrhages	..	..	..	+	..	+	+	+	..	..	+
Alveolar edema	..	+	+	+	+	+	+	+	+	..	+
Bronchopneumonia, early	+	..	+	..	..	..	..	..	..	..	+
<b>Liver:</b>											
Dilatation central veins and sinuses	+	+	+	+	+	+	+	+	+	+	+
Phagocytosis of erythrocytes	..	+	+	+	+	+	+	+	..	+	+
Congestion, general	+	+	+	+	+	+	+	..	+	+	+
Central necrosis	..	..	..	..	..	..	..	+	+	+	+
Portal fibrosis	..	..	..	..	..	..	+	+	+	+	+
Fatty infiltration	+	+	+	+	+	+	+	+	+	+	+
Fatty degeneration	..	..	..	..	..	..	..	+	..	+	+
<b>Spleen:</b>											
Fibrosis of capsule and trabeculae	+	+	+	+	+	+	+	+	+	+	+
"Pooling"	+	+	+	+	+	+	+	+	+	+	+
Phagocytosis of erythrocytes	..	+	..	+	+	..	..	..	..	+	+
Hemorrhage and thrombosis	..	..	..	+	..	..	..	..	..	+	+
Calcium deposits	..	..	..	+	..	+	..	..	..	+	+
Iron deposits	..	..	..	+	..	+	..	..	..	+	+
<b>Kidneys:</b>											
Vessel congestion	+	+	+	+	+	+	+	+	+	+	+
Interstitial edema	..	..	..	..	..	+	+	+	..	+	+
Thrombosed glomeruli	..	..	..	..	..	..	+	+	..	..	..
Medullary fibrosis	..	+	+	..	..	..	+	+	..	..	..
Granular degeneration of tubules	+	+	+	+	+	+	+	+	..	+	+
Pigment in tubule cells	+	+	+	+	+	+	+	+	+	+	+
Calcium in tubule cells	+	..	+	+	+	+	+	+	+	+	+
Casts	..	..	..	..	..	..	+	..	..	+	+
<b>Lymph nodes:</b>											
Hyperplasia and edema	+	+	+	+	+	+	+	+	+	+	+
Phagocytosis of erythrocytes	..	+	+	+	+	+	+	+	+	+	+
Endothelial swelling	..	..	+	+	+	+	..	+	..	..	..
<b>Gastro-intestinal tract:</b>											
Edema of mucosa	+	+	..	..	+	..	..	..	..	..	..
Congestion of mucosal capillaries	+	+	..	..	+	..	+	+	+	+	+
No sections	..	..	+	+	..	+	+	+	+	+	+
<b>Bone marrow:</b>											
Hyperplasia, erythrocytic series	..	+	..	..	+	+	+	+	+	..	..
Phagocytosis of erythrocytes	..	+	..	..	+	..	+	..	..	+	+
No sections	+	..	+	+	..	..	..	..	..	+	+

*Liver.* In the liver no changes were encountered that have not been described before.

*Lymph Nodes.* The lymph nodes showed marked hyperplasia of the reticulo-endothelial cells with extensive phagocytosis of sickled erythrocytes. There was likewise marked edema of the stroma and of the endothelial cells lining the sinuses.

*Spleen.* The spleens were enlarged and rubbery in 8 of the 11 cases. They all showed marked pooling and congestion with increased fibrous tissue in the capsules, trabeculae and pulps.

*Kidneys.* The kidneys showed marked capillary congestion, especially in the glomeruli and the medullary portions. One case showed thrombosis of the glomerular capillaries. There were granular degenerative changes and pigment deposits in the tubules and in 4 cases (ages 0.66, 1.5, 2.25 and 3.65 years) there was calcification of the degenerating tubule cells.

**Discussion.** CLINICAL PICTURE. A study of these case reports reveals a striking clinical picture of the so-called abdominal crisis in sickle cell anemia, terminating fatally in these instances. It may be summed up as follows: the sudden onset of distress or pain in the abdomen usually accompanied by nausea and vomiting; rigidity or tenderness in the abdomen with occasionally pain or tenderness in the muscles and bones of the extremities not involving the joints; malaise, severe chill followed by fever, most frequently jaundice, early rather rapid peripheral vascular collapse with tachycardia, weak pulse, hyperpnea, and signs of central nervous system involvement. The nervous system symptoms may begin suddenly as a convulsion, usually Jacksonian in character, or may be manifested by symptoms of irrational behavior merging into stupor and coma. Nystagmus was a frequent finding. In Case 6 there was no nausea or vomiting and no abdominal rigidity or tenderness could be found; this patient started his fatal illness with central nervous system symptoms.

At the time these patients were seen the blood showed a severe normochromic anemia with hemoglobin values ranging from 11 to 55% (Sahli). The erythrocytes were usually below 2,000,000 per c.mm.; in Cases 6 and 11 they were below 1,000,000 per c.mm. There were no erythrocyte determinations made in Cases 2, 3, 7, 8 and 9. There was a marked leukocytosis present ranging from 15,000 to 83,500 per c.mm. with a marked increase in the absolute number of mononuclear cells. Nucleated erythrocytes were a constant finding and sickled forms of erythrocytes were noted in 5 of the 7 cases (Cases 1, 4, 6, 8 and 10) in which it was possible to obtain differential smears and probably were present in the 2 cases not so noted. The icterus index was increased where taken, ranging from 10 to 40 units. There was nothing consistent in the urinalyses that were obtained, although only routine chemical examinations were performed.

The clinical picture of these cases is remarkably similar to Wintrobe's<sup>2</sup> description of the symptoms of rapid destruction of blood. He states "Rapid destruction of blood is associated with aching pain in the back, abdomen or limbs, headache, malaise and a severe shaking chill, followed by fever. Profound prostration and shock may occur. The cause of the shock is not clear but one of the important factors in its production may well be a reduction in total blood volume resulting

from the rapid destruction of red cells and their removal from the circulation . . . . It appears that the greatest proportion of the products of red cell destruction is neither left in the circulation or excreted by the kidneys but is rapidly removed by the body tissues."

In the records of these cases different physicians made a diagnosis of shock in 5 of the 7 cases (Cases 1, 4, 8, 10 and 11) in which they were seen alive. In Case 4 there is some evidence of hemoconcentration terminally; in Case 5 it is possible that during the previous admission the patient was relieved of shock by the transfusion which was followed by striking improvement. In none of these cases were blood studies done to determine the presence of hemoconcentration.

The cause of the symptoms outlined above is not felt to be rapid destruction of erythrocytes but the rapid removal of erythrocytes from functional status due to an increase in number of sickled forms, stagnation in capillaries, hemoconcentration and shock as discussed later. Likewise, there is no evidence of intravascular hemolysis in these cases.

Yater and Mollari<sup>4</sup> reported a case of sickle cell anemia in a 25 year old Negress who had been hospitalized 6½ weeks for pain in the legs and 3 weeks before death had a spontaneous miscarriage of a 6 month fetus. Vomiting started 18 hours before death, with severe pain in the region of the liver, marked shock and death. At autopsy small, probably old, infarcts were found in the kidneys and spleen; a questionable thrombus was found in the hepatic artery although no microscopic evidence of liver necrosis was present. The evidence for arterial thrombosis of the liver was doubtful by the authors' own admission and it seems possible that their case may have been one of the abdominal crisis dying in shock similar to those presented above.

In Leivy and Schnabel's<sup>5</sup> report of 3 clinical cases of abdominal crisis in sickle cell anemia, 1 case, a 4 year old Negress, was relieved of the abdominal pain in 3 successive admissions by blood transfusions; the last time a splenectomy was performed. The patient returned on 3 occasions following the operation with the same complaints and was relieved each time by blood transfusions. The spleen removed at operation weighed 200 gm. and showed no evidence of infarction. From a study of the reported cases they felt that the liver and gall-bladder could be eliminated as a factor in the production of the symptoms of abdominal crisis. In the first case they reported, a Negro male, aged 29 years, there were marked bony changes in the vertebræ and they suggested root pains as a possible cause for the abdominal crisis although they felt that probably no single explanation would be adequate in all cases.

Campbell,<sup>6</sup> stressing the difficulty of distinguishing between abdominal crises and surgical conditions in the abdomen, reported 6 cases. He states that the most widely accepted theory in explaining the condition is that the pain is caused by splenic infarction or perisplenitis even though there were reports that the pain recurred following splenectomy.

A discussion of the autopsy findings in these cases must be divided into two phases: the changes due to sickle cell anemia and those as a result of the shock present.

**PATHOLOGIC CHANGES DUE TO UNCOMPLICATED SICKLE CELL ANEMIA.** *Brain.* In this group of cases the consistent changes were vessel engorgement, perivascular fibrosis and edema, hyaline changes, endothelial swelling and proliferation, marked congestion, small hemorrhages, focal areas of pyramidal cell degeneration with gliosis, and in some cases corpora amylacea formations. There was also conglutination of erythrocytes and early cellular infiltrations around the vessels. In 1 case there was actual vessel thrombosis.

*Spinal Cord.* In 3 of the 11 cases presented the spinal cords were available for study. There were no degenerative changes found in the cords or in the spinal nerves arising from the cords. The vessels showed some congestion with sickled erythrocytes but no degenerative changes were present in the vessel walls.

Hughes *et al.*<sup>7</sup> reported the autopsy findings in the brains of 2 cases of sickle cell anemia. One case, a 6 year old male, had cerebral symptoms from 20 months of age and died with aphasia, stupor and a residual paralysis from an attack at the age of 3 years. At autopsy there was atrophy of the right cerebral cortex probably due to thrombosis of the right middle cerebral artery, dilatation of the ventricles, chronic adhesive leptomeningitis, acute hemorrhagic leptomeningitis and recent thrombosis of the left middle cerebral artery with early encephalomalacia. The second case, a 26 year old male, had had a "stroke" at the age of 6 years and residual paralysis since then. At autopsy atrophy of the left cerebral cortex, old meningeal and subpial hemorrhages, multiple old subpial cysts, chronic adhesive arachnoiditis, and uremia were found. They felt that the lesions were primarily intravascular with subsequent thrombosis, hemorrhage, and degenerative changes.

Connell<sup>8</sup> reported a case of cerebral necrosis due to "sickle cell disease" in a 20 year old Negress with a history of left-sided paralysis starting 6 years before. At autopsy there was old right cerebral atrophy and also a recent massive left cerebral hemorrhage; histologic study revealed atrophic changes in the pyramidal cells; the vessels showed endothelial cell proliferations, hyaline changes, congestion and thrombosis; there were scattered corpora amylacea throughout the sections.

Bridgers<sup>9</sup> reported 2 cases of cerebral changes in sickle cell anemia. One case, a 62 year old Negress, was in shock and stupor for 3 days before death; autopsy revealed multiple focal necroses and hemorrhages in the brain which were associated with "peculiar hyaline bodies resembling masses of fluid and blood cells within greatly congested capillaries." This case is well beyond the usual accepted age for active sickle cell anemia. The other case, a 4 year old Negress with an old history of paralysis, showed a massive recent hemorrhage with areas of encephalomalacia and some areas of old atrophy. Histologic examination in this case showed old partial occlusion of the larger arteries, fragmentation of the elastic lamina, endothelial proliferations, hyaline vessel changes and some inflammatory cell infiltrations. Case 5 of the series reported here showed the same extreme endothelial proliferations,

old thromboses of medium sized arteries, and focal pyramidal cell degenerations and gliosis. It is interesting that this case had an episode of cerebral symptoms 2 months before, which was terminated clinically by a transfusion. There were no residual symptoms demonstrable; the patient was admitted with the same severe symptoms the last time and expired.

Wertham *et al.*<sup>10</sup> studied 5 cases of sickle cell anemia and give the following conclusions: "The essential neuropathologic features of sickle cell anemia are small necrotic and necrobiotic lesions on a vascular basis, diffusely distributed, with predilection for the border between the cortex and the subcortical white matter; marked general hyperemia and congestion of blood-vessels; hypertrophy and proliferation of endothelial and adventitial elements of the walls of small blood-vessels; siderotic pigment in intra-adventitial spaces and adventitial cells; larger vascular lesions of uncharacteristic type (softenings, thromboses, etc.); small hemorrhages and extravasations; intravascular lipoid material and fat embolism of capillaries and precapillaries; focal and diffuse changes in the nerve cells in cortical and subcortical gray structures, and focal areas of demyelination in the spinal cord, similar to those seen in subacute combined degeneration." Their conclusions are open to question along the following lines: the ages studied were 28, 31, 49, 56 and 65 years; the last 3 are well beyond the usual age of active sickle cell anemia and in none of their cases are any hemograms given. In 2 of the 3 oldest patients a diagnosis was made of arterio- and arteriosclerosis with hypertension. The patient, aged 31 years, had a ruptured congenital cerebral aneurysm on the left side and a similar unruptured aneurysm on the right side. The lipoid material found in the capillaries in the 2 cases was not explained as to source and they did not demonstrate foci of necrosis in the bone marrow. The spinal cord changes described were found in only 1 case, not identified, and the clinical data given with the cases makes no mention of spinal cord symptoms, abdominal pain, or the other manifestations of crises in sickle cell anemia. Likewise the symptoms of combined degeneration of the spinal cord according to Wechsler<sup>11</sup> are paresthesias, "tabetic" ataxia and rarely pains, although girdle sensations do occur. Wechsler says that in his experience pernicious anemia is the only condition in which combined degeneration occurs, with the possible exception of tetanias.

Wade and Stevenson<sup>12</sup> reported a case of sickle cell anemia in which fat emboli from necrotic foci in the bone marrow produced focal hemorrhage and necrosis in the brain. They, however, mention that Lehman and McNattin found fat emboli in 37 of 50 autopsies and that Vance found it in 7 of 82 cases definitely not associated with trauma or bone marrow necrosis. They felt that in their case of sickle cell anemia the fat emboli were of importance in producing symptoms and the cerebral changes.

*Heart.* Myocardial hypertrophy was present in 8 of the 11 cases and has been described by Klinefelter.<sup>13</sup> However, he mentions no histologic changes beyond myocardial fiber hypertrophy. Steinberg<sup>1</sup>

mentions frequent observations of patchy fatty degeneration in the myocardium of the cases he reviewed. In these cases muscle fragmentation, fatty changes, scarring, granular degeneration and edema were a constant finding. In 3 cases there were perivascular cell infiltrations; whether these were due to the anoxemia and stagnation of sickle cell anemia or shock or both is difficult to determine. From the relatively advanced changes present it is felt that they may have been a result of the sickle cell anemia. No valvular or endocardial changes were present in any of the cases.

*Lung.* In these cases there was no histologic evidence of vessel thrombosis, sclerosis or infarction. It is possible that death intervened too rapidly for the production of such changes in these cases; likewise the erythrocytes in the lungs would be obviously better oxygenated than elsewhere and the changes in the vessels due to anoxemia would be longer in starting. Vessel changes, thrombosis and infarction have been described by Yater and Hansmann<sup>14</sup> and Steinberg,<sup>1</sup> although their cases were in the older age groups and had more chronic illnesses in the terminal pictures.

*Kidneys.* In the kidneys calcification of degenerating tubular epithelial cells has been described in 1 case by Yater and Mollari<sup>4</sup> and was present in 4 of these cases.

Extensive erythrophagocytosis was present in the liver, lymph nodes, spleen and bone marrow of most of these cases. This has been adequately described before, but in view of its probable importance should be stressed again.

**PATHOLOGIC CHANGES DUE TO NON-TRAUMATIC SHOCK.** The gross and microscopic findings in shock have been described by Moon.<sup>15</sup> In the 11 cases presented here the gross findings (Table 2) of collapsed peripheral veins, peripheral edema, thick, dark unclotted blood, cerebral congestion and edema, effusions into the body cavities, pulmonary congestion and edema, congestion and edema of the gastro-intestinal tract, and marked congestion of the liver, kidneys and spleen fit his gross picture of shock.

The microscopic changes that are found in shock not complicated by toxemia consist of marked capillary congestion, edema and some petechial hemorrhages with parenchymatous changes in the liver and kidneys if the condition is marked. The heart usually shows only congestion. In these cases (Table 5) the congestion was intense, edema marked, and granular degenerative changes were present in the liver and kidneys. It is felt, as stated before, that the myocardial changes were of considerably longer duration than the shock and probably represent changes due to the sickle cell anemia.

In Table 4 are given the postmortem blood non-protein nitrogen, urea nitrogen and creatinine levels. They are available in 8 of the 11 cases and show nitrogenous retention as Moon describes being present in shock.

The marked leukocytosis found in these cases ranging from 15,000 to 83,600 per c.mm. in the absence of infection clinically or at autopsy is strong evidence for shock. Moon gives a résumé of the literature on this subject.



**MECHANISM OF THE PRODUCTION OF SHOCK.** The absence of trauma and infection in the clinical records and at the postmortem examinations of these cases rules out shock from these causes. There is left shock due to a lack of normally functioning erythrocytes. The shock in these cases is obviously not due to hemorrhage and it is not due to intravascular hemolysis because of the constant failure to demonstrate hemoglobinuria in these cases. Haden<sup>16</sup> says that the failure to demonstrate hemoglobinuria is definite evidence that erythrocyte destruction is taking place in the reticulo-endothelial cells of the body and not in the blood stream. Although Sydenstricker<sup>17</sup> reported auto-agglutination *in vitro*, Cardoza<sup>18</sup> showed that the sickling trait was not connected with any one of the isohemagglutinin or immune agglutino-gen groups, and he could not isolate any anomalous isohemagglutinins among the cases he studied.

Wiggers<sup>19</sup> states that in the anemic type of anoxia "the oxygen tension is normal but the supply of (oxygen) is deficient owing to a decreased quantity of functional hemoglobin." Best and Taylor<sup>20</sup> discussing this say that the heart rate is increased under these circumstances, thus increasing the rate of blood flow in order that the oxygen delivered in small quantities in anemia may be delivered at the high pressure necessary for tissue oxygenation. Karsner<sup>21</sup> says that anemia produces changes in the myocardial fibers which tend to lessen the blood pressure and thus the blood volume flow in many cases, and certainly in the cases reported here the changes he described were present.

In sickle cell anemia the anemia is constant though somewhat variable in intensity of symptoms. Hahn and Gillespie<sup>22</sup> feel that in the sickled forms of erythrocytes the hemoglobin is in a reduced or uncombined form; if this is true that amount of hemoglobin present in the sickled erythrocytes is of no value for oxygen carbon dioxide carriage in a person already suffering from a lack of hemoglobin. Numerous studies have been published upon the influence of oxygen and carbon dioxide concentrations in sicklemia and sickle cell anemia. *In vitro* studies by Hahn and Gillespie,<sup>22</sup> Scriver and Waugh,<sup>23</sup> and Tomlinson<sup>24</sup> have shown that a reduction of oxygen concentration, an increase of carbon dioxide concentration or the simultaneous change of both produces an increase in the number and degree of sickled erythrocytes. The rapid methods for diagnosing the sickling phenomena by Scriver and Waugh through stagnation of blood in the finger tip and my method of exposing blood to carbon dioxide in a separatory flask are based upon these factors. *In vivo* studies by Klinefelter<sup>25</sup> showed that a reduction of the oxygen content in arterial blood increased the percentage of sickled cells. Using a patient with sickle cell anemia, not in a crisis, the resting control study showed 19% sickled cells in arterial blood; after the administration of 100% oxygen for 20 minutes there were 9.5% sickled cells; after the administration of 10% oxygen for only 10 minutes there were 32% sickled cells in the arterial blood which represents a marked increase in sickled forms for a drop of approximately 10% oxygen concentration from that of nor-

mally inspired atmospheric air. Hahn<sup>25</sup> believes that there is a correlation between the severity of the sickle cell anemia and the number

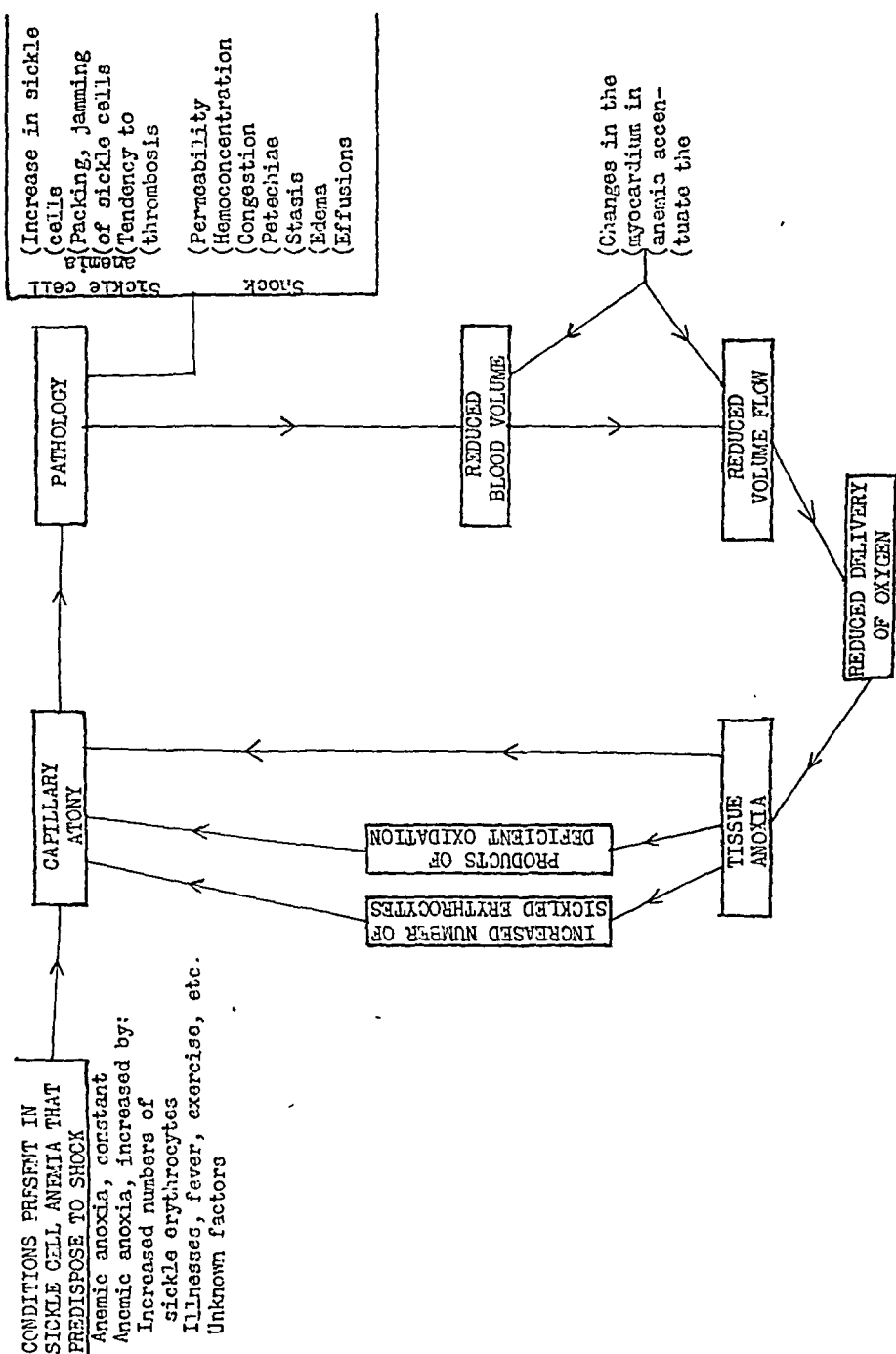


Fig. 1.—Suggested mechanism of the production of shock in sickle cell anemia. (Modified from Moon<sup>15</sup>)

of sickled cells in the circulation and Sherman<sup>26</sup> uses the presence of sickled forms in the circulation as a means of differentiating between sickle cell anemia and sicklelemla.

It is my belief that under certain conditions, as yet imperfectly known, the anoxia which accompanies active sickle cell anemia probably precipitates a chain of events that frequently results in shock. The conditions that may bring about this change may be the severe anemia (less than 1,000,000 erythrocytes per c.mm. for example), failure of the circulation due to cardiac damage, increased demand upon the oxygen-carrying capacity of the blood by fevers, illnesses, exercise, and so forth, and finally those as yet unknown factors that produce marked erythrocytic destruction in these cases or that increase the number and degree of sickled forms in the circulation and thus lessen the functional hemoglobin present. The mechanism is shown diagrammatically in Figure 1.

With the circulating sickled erythrocytes present in sickle cell anemia we can presume that there are certain degrees of anoxia present in the tissues, especially in the arterial and venous capillaries where the blood is considerably removed from its point of oxygenation.

Krogh<sup>27</sup> and Landis<sup>28</sup> have shown that capillary anoxia results in damage to the lining cells rendering them more permeable to plasma; the escape of plasma produces hemoconcentration which tends to stagnate the blood, slow the circulation through the small vessels and intensify the anoxia while building up the carbon dioxide content which would tend to cause sickling in any susceptible erythrocytes not already showing the change. Diggs and Ching<sup>29</sup> have described as a prominent feature in the microscopic examination of tissues from sickle cell anemia cases "the prominence of capillaries, which are dilated and filled with sickled cells, giving the appearance of packing under pressure. . . . A possible explanation of the capillary engorgement is that the elongated and spiked cells interlock and pass with more difficulty through narrowed spaces than do normal cells." Considering the possibility of shock being present in these cases, the appearance of packing or jamming may be due to both the hemoconcentration and the abnormal shapes of the erythrocytes. In either event, it is marked in the microscopic examination of sickle cell anemia tissues and the stagnation of blood in the dilated, atonic and damaged capillaries removes considerable numbers of erythrocytes from the circulating blood volume. This tends to accentuate the circulatory deficiency and thus increase the anoxia and intensify the vicious cycle of shock which when continued for a relatively short period of time will terminate fatally with the morphologic changes of shock described by Moon.<sup>15</sup>

There are two other findings in these cases which may play some part in accentuating the shock when it is initiated. Moon<sup>15</sup> has shown that the spleens of dogs in experimental shock, and to a lesser extent in humans, are contracted and relatively bloodless. In these cases of sickle cell anemia there was considerable thickening and fibrosis of the capsules and trabeculae with scarring of the reticular framework and pulp (presumably the result of previous episodes); such changes would tend to make the spleens less contractile and prevent the accumulation and discharge of any reserve erythrocytes present in the spleens. In spite of the fibrosis, there was often con-

gestion and pooling in the sections; grossly the spleens were usually enlarged, firm and rubbery. In cases where the spleen was atrophic and small, there would obviously be no reserve of erythrocytes. The other finding is the extensive phagocytosis of sickled erythrocytes by the reticulo-endothelial cells, especially in the liver and lymph nodes, and less marked in the spleen and bone marrow. The exact part this may play is hard to evaluate; however, it does remove some erythrocytes from the deficient and failing circulation. Likewise, the extensive erythrophagocytosis may be one of the factors initiating or participating in the accentuation of the anemia and thus starting the cycle of anoxia that may end in shock.

**Comment.** In the cases presented here, shock resulting from the anoxia accompanying anemia is felt to play an important part in their symptomatology and deaths. Whether shock enters into the clinical picture of other manifestations of sickle cell anemia will await corroboration by other investigators. The cases of sickle cell anemia seen with acute symptoms by any one person are relatively few in short periods of time; however, if everyone remains aware of the possibility of shock and uses the means available to determine the presence of shock, the validity of the explanation given here will be rapidly checked. Likewise a therapeutic aid in the treatment of severe sickle cell anemia will be available in the use of blood transfusions and plasma to treat the shock. In regard to blood transfusions the sickling of erythrocytes in the usual stored blood from sicklemic individuals and reactions resulting from the use of this blood must be kept in mind, as has been previously described.<sup>24</sup>

**Summary.** Analysis of 11 cases of abdominal crises in uncomplicated sickle cell anemias showed that 4 cases were dead on arrival at the hospital, or died before they were seen by a physician. Of the 7 cases examined during life notation was made that 5 were in shock. The clinical picture was as follows: sudden onset of distress, pain, rigidity or tenderness in the abdomen usually accompanied by nausea and vomiting, occasional pain or tenderness in muscles and bones, severe malaise, chill, and fever; frequent jaundice, early rapid peripheral vascular collapse with shock and central nervous system involvement. Clinical laboratory studies of these cases revealed severe normochromic anemias (hemoglobin 11 to 55% Sahli), erythrocytes 0.59 to 2.4 million per c.mm.) and marked leukocytosis (15,000 to 83,600 per c.mm.), with an absolute increase in mononuclear cells; nucleated erythrocytes and sickled forms were an almost constant finding and the icterus indices were increased (10 to 40 units).

Postmortem examinations, with special attention to the changes of sickle cell anemia in a young age group with no complicating illnesses, revealed congestive and degenerative changes in the capillaries and small venules of the brain, pyramidal cell degeneration, glial proliferation, and corpora amylacea formations. No spinal cord changes were found beyond vessel congestion. In the hearts there were hypertrophy, fatty changes, albuminous degeneration, edema and fragmentation of the myocardial fibers; 3 instances of vessel degenera-

tion and perivascular cell infiltrations were present. No endocardial or valvular lesions were found. No changes were found in the lungs beyond marked capillary congestion. The livers showed marked congestion and extensive phagocytosis of sickled erythrocytes by the reticulo-endothelial cells and the same findings were present in the lymph nodes. The spleens were enlarged in 8 of the 11 cases and showed marked congestion and "pooling," together with fibrosis of capsule, trabeculae and reticular stroma. The kidneys showed marked congestion of the capillaries with glomerular thrombosis in 1 case. The tubules showed granular degenerative changes, pigment deposits, and calcification in 4 cases.

Postmortem examination likewise revealed the following evidence of shock: collapsed peripheral veins, peripheral edema, thick, dark, unclotted blood, cerebral congestion and edema, effusions into the body cavities, pulmonary congestion and edema, congestion and edema of the gastro-intestinal tract with marked congestion of the liver, spleen and kidneys. Autopsy blood chemical determinations showed nitrogen retention. The spleens were enlarged, engorged and fibrosed, which probably prevented them from contracting in shock.

The clinical symptoms at the onset of abdominal crises in sickle cell anemia are remarkably similar to Wintrobe's<sup>2</sup> description of the symptoms of rapid destruction of blood. There is no evidence of extremely rapid blood destruction in these cases; it is felt that the symptoms are due at first to increases in the number of sickled cells and their removal from the circulation with rapidly developing shock producing the terminal symptoms and death.

It is suggested that the mechanism of death in these cases of abdominal crisis in sickle cell anemia is shock. A possible explanation for the shock is: the anoxia accompanying anemias is increased in severity in sickle cell anemia as sickled erythrocytes do not carry or are poor carriers of oxygen to the body tissues; the heart in severe anemia is weakened; sickled erythrocytes have a tendency to pack or jam in small capillaries; the capillary anoxia results in plasma loss, hemoconcentration, stagnation, and the stagnation removes available erythrocytes from the circulation, increasing the circulatory failure, anoxia, and perpetuates the vicious cycle of shock.

Further examination of cases of abdominal crisis and other conditions in sickle cell anemia should be directed toward determining the presence of shock. If shock is present, transfusions and plasma may greatly alter the clinical picture. Transfusions in these cases must not be given from people showing the sickling trait.

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## THE ARTIFICIAL PRODUCTION AND SIGNIFICANCE OF TARGET CELLS

### WITH SPECIAL REFERENCE TO THEIR OCCURRENCE IN THALASSEMIA (COOLEY'S ERYTHROBLASTIC ANEMIA)

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HADEN and Evans<sup>6</sup> in 1937 first noted in fresh preparations of the blood of patients with sickle cell anemia considerable numbers of erythrocytes which "instead of being biconcave disks had a central 'sugar loaf' elevation so that a cross-section had the appearance of a Mexican hat instead of a dumbbell." Such RBC in stained smears appeared to have a peripheral ring and central dot of hemoglobin separated by an intervening zone of pallor. In some, a bridge of hemoglobin connected the central dot with the peripheral ring. These they referred to as "dimpled corpuscles" and erroneously considered them to occur in significant numbers only in sickle cell anemia.

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In 1938 Barrett,<sup>1</sup> in reporting an extensive series of observations on this type of erythrocyte, introduced the term "target corpuscles," a reference only to their appearance in the stained smear and not to their three-dimensional form. He found this type of erythrocyte with considerable frequency in the blood of patients with biliary obstruction, steatorrhea, certain hypochromic anemias, as well as after splenectomy, and observed large numbers of these cells in jaundiced patients in whom there was no abnormality of the erythrocyte count or hemoglobin value. Experiments were conducted which indicated that the target corpuscles were appreciably more resistant to hemolysis in hypotonic solutions of sodium chloride than were normal erythrocytes. From studies on fresh preparations and cells fixed with formol saline, Barrett concluded that the three-dimensional precursor of the target cell was probably a bowl-shaped corpuscle with a central evagination accounting for the central dot of hemoglobin. Roentgenograms of plasticine models were offered as corroborative evidence that such "umbonate" cells would appear as targets when viewed in transmitted light.

Dameshek<sup>3</sup> confirmed the presence of target cells in conditions other than sickle cell anemia. He and others<sup>8,12</sup> noted their presence in thalassemia major<sup>9</sup> (erythroblastic anemia of Cooley, Mediterranean anemia), and in the milder, genetically related anemia for which the name "thalassemia minor" has recently been proposed.<sup>9</sup> The latter has been shown to be qualitatively similar to the full-blown disease, but quantitatively less severe, and represents the reservoir of genetic carriers who perpetuate the fatal form of the malady. Dameshek<sup>4</sup> referred to anemias of this milder type as "Mediterranean Target-Oval Cell Syndromes," and suggested the possibility that the target cell may be "the inherited factor responsible for the disease known in its full-blown form as Cooley's erythroblastic anemia." Smith<sup>8</sup> has taken exception to this viewpoint, and has concluded that the target cell should be regarded as non-specific.

Bohrod<sup>2</sup> in 1941 suggested that the target cell was merely a young, resistant cell, basing his conclusion on observation of the appearance of target cells in the early days after a brisk hemorrhage, and the presence of target forms among the larger, basophilic, and presumably younger cells seen at this time. He concluded that this type of erythrocyte appeared following blood loss regardless of source, and that these cells might be constantly present if blood loss were constant.

Greenblatt<sup>5</sup> reported in 1943 on the occurrence of a high percentage of target cells in the peripheral blood of a large number of soldiers with acute hepatitis and icterus. During the time target cells were present there was also increased erythrocyte resistance to hypotonic solutions of sodium chloride. As the icterus decreased there was likewise progressive reduction in the number of target corpuscles in the peripheral blood, but no definite correlation between the severity of icterus and the numbers of target cells present could be made.

Because of our particular interest in the target corpuscle in thalassemia major and minor, a group of experiments bearing on the artificial production and nature of the target cell was undertaken.

**Methods.** In every experiment, blood was obtained from the antecubital vein in a clean, dry syringe without stasis. Control blood was in every instance placed in a bottle containing a mixture of 40% potassium oxalate and 60% ammonium oxalate. When exactly 5 cc. of blood was added to such containers a 0.2% concentration of the anticoagulant mixture resulted. Heller and Paul<sup>7</sup> have shown that under these conditions there is no alteration in erythrocyte volume. In preliminary experiments, we found that the appearance of the erythrocytes in numerous blood smears made after a short time interval from samples so collected differed in no wise from those in smears made directly from peripheral blood. The containers employed for such control samples will be referred to hereafter as "control hematocrit bottles." All serum and plasma chloride determinations were done by the micro method of Van Slyke.<sup>10</sup> Whenever the volume of packed erythrocytes was determined, a Wintrobe hematocrit tube properly filled with a thoroughly mixed sample of blood was centrifuged for 1 hour at 3000 r.p.m. All smears were made by the coverslip method and stained with Wright's stain.

**Presentation of Data.** EXP. 1. This experiment was designed to determine whether the erythrocytes of normal individuals can readily be converted to target cells if the blood is rendered hypertonic by the addition of potassium oxalate.

Potassium oxalate bottles were prepared as follows: 1 cc. of 2% potassium oxalate solution was pipetted into thoroughly cleaned bottles and the solution dried so that each bottle contained 0.02 gm. potassium oxalate. In a preliminary experiment, 3, 5 and 7 cc. of blood from a normal individual was placed in such bottles. It was found that the largest percentage of target cells in stained smear was present in blood from the bottle in which 3 cc. had been placed. Accordingly, blood was drawn from 6 normal individuals, and in each instance 3 cc. was added to a potassium oxalate bottle prepared as described above. At the same time 5 cc. of the same blood was added to a control hematocrit bottle. Smears were made from both control and experimental blood and the appearance of the erythrocytes compared. In every case, there were large numbers of target cells present in the hypertonic blood, and only a very scattered few or none in the control.

TABLE 1.—EFFECT OF THE ADDITION OF POTASSIUM OXALATE TO BLOOD ON THE MORPHOLOGY, VOLUME AND RESISTANCE TO HYPOTONIC SALINE OF NORMAL ERYTHROCYTES

Name	Smear	Presence of target cells	Vol. packed RBC	- % shrinkage	Hemolysis in hypotonic saline	
					Begins (%)	Complete (%)
G. B.	Exp. blood	Many	..	..	.48	.30
	Control blood	1 seen	..	..	.48	.30
L. Y.	Exp. blood	Many	..	..	.50	.32
	Control blood	None	..	..	.48	.32
W. G.	Exp. blood	Many	39.8	15.3		
	Control blood	Very rare	47.0			
C. K.	Exp. blood	Many	39.0	15.6		
	Control blood	None	46.2			
W. W.	Exp. blood	Many	37.3	18.6		
	Control blood	None	45.8			
L. F.	Exp. blood	Many	38.5	16.3		
	Control blood	None	46.0			

In some instances, fragility tests were performed on both hypertonic and control blood, while in others the volume of packed erythrocytes



was determined on both samples. Results are summarized in Table 1. The target cells produced in this manner showed no increased resistance to hypotonic solutions of sodium chloride.

EXPERIMENT 2. In this experiment, an attempt was made to determine whether other agents causing hypertonicity were equally effective in producing target cells, or whether the target corpuscles produced in Experiment 1 were the result of some property of potassium oxalate rather than of simple changes in tonicity.

Ten cc. of venous blood was drawn from several normal individuals; 5 cc. was allocated to a control hematocrit bottle. The remaining 5 cc. was added to a second bottle differing from the control container solely in the addition of 15 mg. of dry sodium chloride. Smears were obtained from both samples, and the volume of packed erythrocytes determined as before.

In every case there were large numbers of target cells in the blood to which sodium chloride was added. Results appear in Table 2.

TABLE 2.—EFFECT OF THE ADDITION OF SODIUM CHLORIDE TO BLOOD ON THE MORPHOLOGY AND VOLUME OF NORMAL ERYTHROCYTES

Name	Smear	Presence of target cells	Vol. packed RBC	% shrinkage
W. A.	Exp. blood	Many	41.2	17.3
	Control blood	None	49.8	
F. B.	Exp. blood	Many	37.1	17.0
	Control blood	None	44.7	
A. R.	Exp. blood	Many	37.0	16.1
	Control blood	None	44.1	

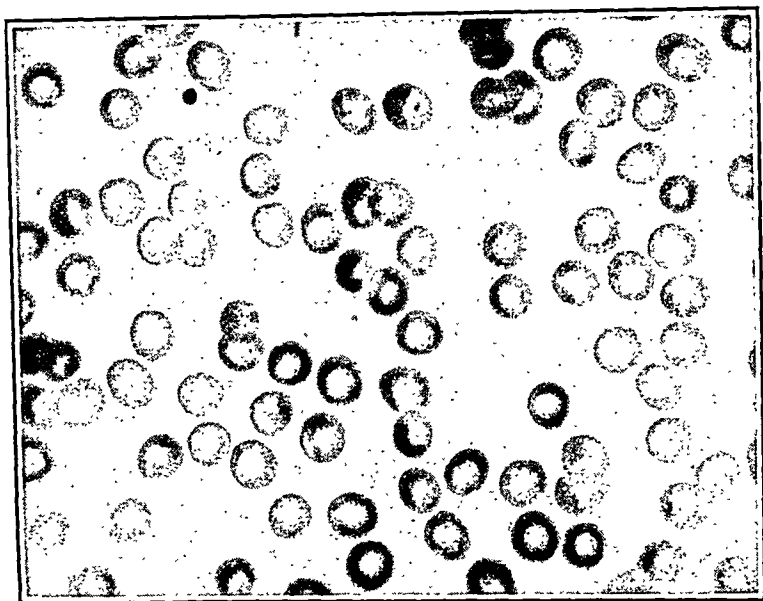
EXPERIMENT 3. This experiment was designed to determine whether the erythrocytes of normal individuals can readily be converted to target cells by suspending them in serum rendered hypertonic by simple evaporation and without the addition of chemicals.

TABLE 3.—EFFECT ON MORPHOLOGY OF NORMAL ERYTHROCYTES OF SUSPENDING THEM IN CONCENTRATED SERUM OF SAME PERSON

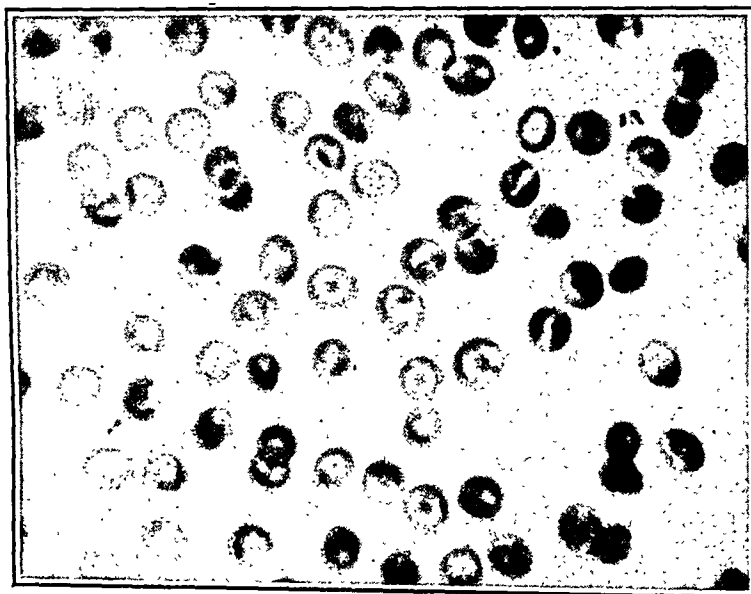
Name	Smear	Presence of target cells	Serum chlorides (millieq.)
J. V. N.	Exp. blood	Many	148
	Control blood	None	107
W. N. V.	Exp. blood	Many	182
	Control blood	None	103

Twenty-five cc. of venous blood was drawn from 2 normal individuals. The blood was allowed to clot, centrifuged, and the serum pipetted off immediately. Ten cc. samples of the serum thus obtained were allowed to evaporate in a watch glass to roughly 80 and 60% of their original volume respectively. A second 5 cc. sample of blood was then collected from the same persons and placed in a control hematocrit bottle. From this blood, smears were made as controls. The control sample was then centrifuged, the normal plasma pipetted off, and replaced with an equal volume of the concentrated serum from the same individual. The cells were resuspended in the concentrated serum and smears were made. Chloride determinations were done in

each case on the normal plasma and the concentrated serum in order to evaluate the degree of concentration. As before, the hypertonic sample contained large numbers of target cells. The results are shown in Table 3. Photomicrographs of control smears and of smears prepared from cell suspensions in the concentrated serum of the same person are shown in Figure 1.



A



B

FIG. 1.—A, Blood smear of a normal individual (J. V. N., Table 3) showing normal erythrocytes and no target cells. ( $\times 970$ .) Serum chlorides, 107 milliequivalents.

B, Smear made from the same blood (J. V. N., Table 3) after the centrifuged erythrocytes were resuspended in the hypertonic concentrated serum of the same person. Note the target cells. ( $\times 970$ .) Serum chlorides, 148 milliequivalents.

EXPERIMENT 4. This experiment was designed to find out if target cells could be produced in the experimental animal as a result of plasma concentration secondary to dehydration.

A 13.65 kg. dog was rapidly dehydrated as follows:\* The animal was first placed for 8 hours in a room in which the temperature was maintained around 115° F. He was then removed to a cool room for 16 hours following which he was subjected to another 6½ hours at 115° F. Blood was removed from a leg vein at the start of the experiment, after 8 hours at 115° F., and again when the dog was removed from the hot room at the conclusion of the experiment. At each bleeding, exactly 5 cc. of blood was placed in a control hematocrit bottle and smears made. The dog was denied fluids throughout the entire experiment.

Results are summarized in Table 4. Significant plasma concentration as evidenced by plasma chloride determinations occurred, though of course this could not be carried to the same extremes as *in vitro* experiments. In blood smears made before dehydration took place only 1 target corpuscle was seen in many random fields. In blood smears made at the time of maximum dehydration an average of 2 to 4 target cells were seen in every high power field with as many as 6 seen in some and as few as 1 in others. Figure 2 shows photomicrographs of blood smears made before and after dehydration.

TABLE 4.—EFFECT OF RAPID DEHYDRATION ON THE MORPHOLOGY AND VOLUME OF ERYTHROCYTES OF THE DOG

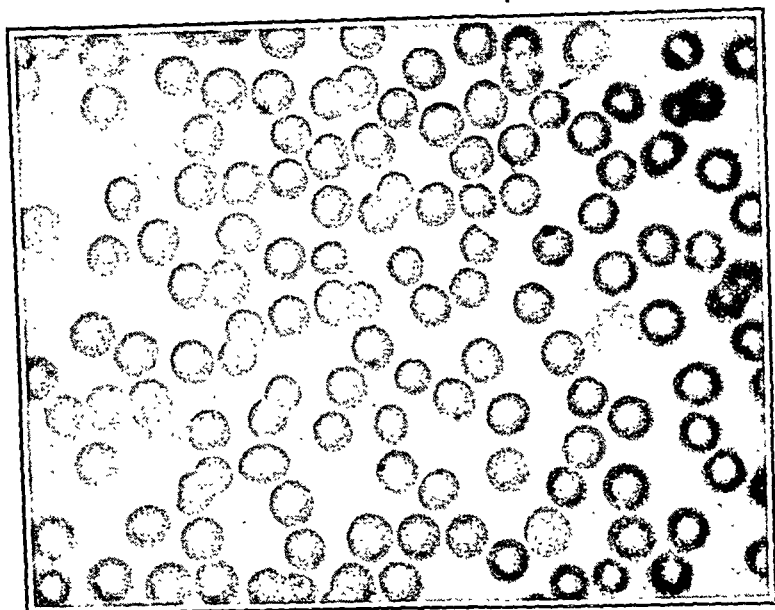
	Elapsed time in hours from start of experiment		
	0 hrs.	8 hrs.	30.5 hrs.
Weight in kg. . . . .	13.60	12.48	11.31
% net weight loss . . . . .	0	8.30	17.00
RBC in millions . . . . .	5.73	6.34	6.99
Hb. in gm. per 100 cc. . . . .	13.40	14.40	15.60
Vol. packed RBC . . . . .	42.50	42.80	45.00
M.C.V. in c.μ . . . . .	74.20	67.50	64.40
M.C.H. in γγ . . . . .	23.40	22.70	22.30
M.C.H.C. in % . . . . .	31.50	33.60	34.70
Plasma chlorides, millieq. . . . .	116	123	124
Smear, target cells . . . . .	Very rare	Av. 1 per h.p.f.	Av. 2-4 per h.p.f.

EXPERIMENT 5. In this experiment, an attempt was made to convert naturally occurring target cells in the blood of a patient with sickle cell anemia to cells of relatively normal appearance by suspending them in the patient's own plasma rendered hypotonic by the addition of distilled water.

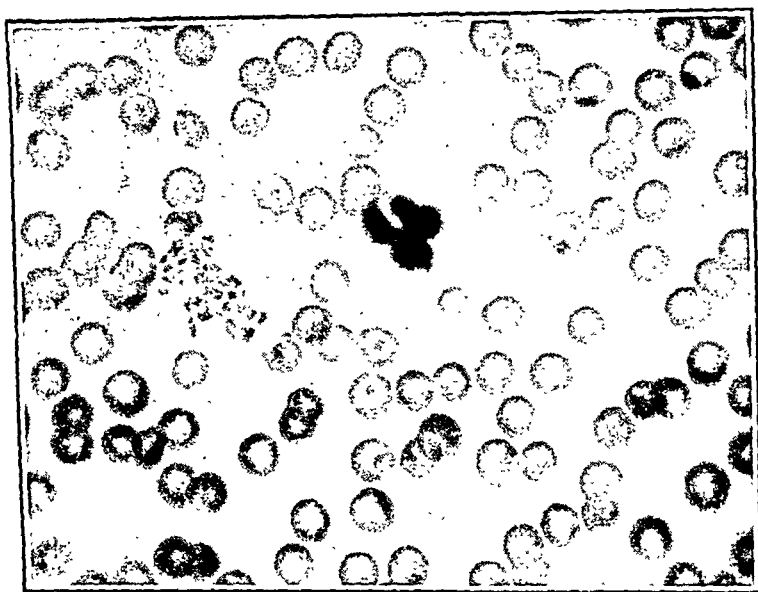
Twenty cc. of venous blood was drawn from M. W. (No. 195904), a patient with sickle cell anemia, whose blood had been found repeatedly to contain large numbers of target cells. Exactly 5 cc. was placed in each of 4 control hematocrit bottles, and control smears were made from one such sample. Three samples were then centrifuged, and as much of the supernatant plasma as possible pipetted off. A plasma chloride determination was done on the first of these to serve as a

\* We are grateful to Dr. E. Adolph for the opportunity of studying this animal during dehydration.

control. The remaining two samples of plasma thus obtained were diluted with distilled water and then added to their respective sedi-



A



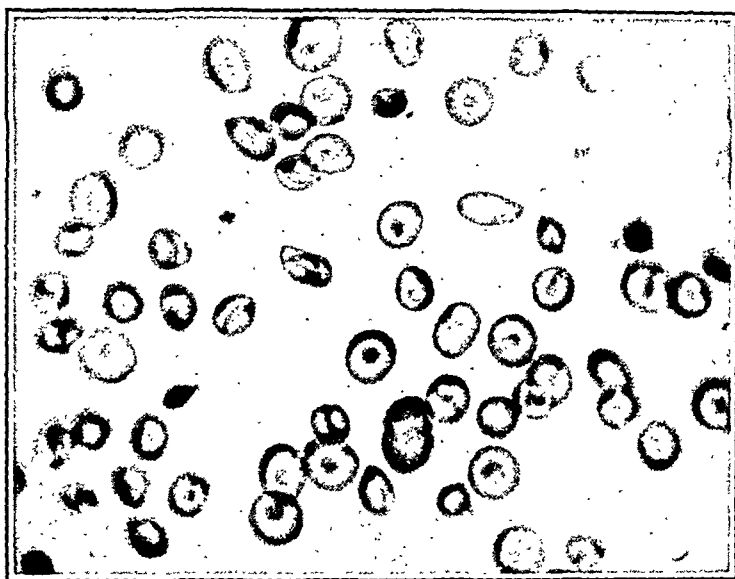
B

FIG. 2.—A, Blood smear before dehydration of experimental dog (Table 4). ( $\times 970$ .) Plasma chlorides, 116 milliequivalents.

B, Blood smear of the same animal after dehydration. The field shown represents an area in which the change was maximal. ( $\times 970$ .) Plasma chlorides, 124 milliequivalents.

ments of red cells in volume equal to the amount of normal plasma previously removed. The cells were resuspended, and smears drawn from this hypotonic blood. These cell suspensions were then recentri-

fuged, the supernatant hypotonic plasma removed, and plasma chloride determinations made on each sample to evaluate the degree of



A



B

FIG. 3.—A, Blood smear of M. W. (No. 195904), a patient with sickle cell anemia. Note the large number of target cells. ( $\times 970$ ) Plasma chloride, 106 milliequivalents.

B, Blood smear of M. W. after suspension of centrifuged erythrocytes in the patient's own plasma rendered hypotonic by dilution with distilled water. Note the almost complete lack of target cells and presence of spherocytes. ( $\times 970$ ) Plasma chlorides, 70 milliequivalents.

dilution. All smears made from hypotonic blood showed a marked reduction in the number of target cells, a marked increase in the num-

ber of cells of relatively normal appearance, and the presence of spherocytes which were not noted in the control smear. The results are shown in Table 4. Photomicrographs of smears made on control and hypotonic blood are shown in Figure 3.

TABLE 5.—EFFECT ON THE MORPHOLOGY OF NATURALLY OCCURRING TARGET CELLS IN SICKLE CELL ANEMIA OF SUSPENDING THEM IN THE DILUTED PLASMA OF THE SAME PERSON

Smear	Presence of target cells	Plasma chlorides (millieq.)
Undiluted control sample . . . . .	Very many	106
Diluted Sample No. 1 . . . . .	Fewer target cells; some spherocytes	75
Diluted Sample No. 2 . . . . .	Only occasional target cells; more spherocytes	70

**Analysis and Interpretation of Data.** Experiments 1, 2 and 3 indicate that artificial target cells indistinguishable in the stained smear from those found in certain pathologic conditions can readily be produced by merely suspending normal erythrocytes in hypertonic plasma or serum. It is immaterial whether the hypertonicity is attained by adding potassium oxalate or sodium chloride to samples of blood, or whether cells are suspended in serum made hypertonic by evaporation without addition of chemicals. Experiment 1 shows that such artificially produced target cells have no increased resistance to hypotonic solutions of sodium chloride, unlike most of those occurring naturally in pathologic states.

Experiment 4 suggests that target cells may be produced *in vivo* in the dog if the plasma can be sufficiently concentrated as a result of rapid dehydration. Here, the plasma of the experimental animal has been rendered hypertonic in comparison with the plasma of the same animal before dehydration. The fact that target cells were not present in such dramatic numbers as *in vitro* experiments is probably due to the limitations in the amount of plasma concentration which can be attained without causing the death of the animal. It seems likely that the degree of cell shrinkage produced *in vivo* in this instance represented approximately the borderline at which the erythrocytes in question first began to assume the form of a target in the blood smear. Further confirming experiments are indicated.

Experiment 5 indicates that target cells occurring in large numbers in a pathologic state, sickle cell anemia, will not appear as targets when suspended in hypotonic plasma.

It is well known that the suspension of erythrocytes in hypertonic solutions results in the loss of fluid from the red blood cell with ultimate crenation, whereas the suspension of erythrocytes in hypotonic solutions results in accumulation of fluid within the cell by a similar process with ultimate lysis. It appears that the artificial target cells produced in Experiments 1, 2, 3 and 4 resulted from cell shrinkage of appropriate degree, and that the disappearance of naturally occurring target cells in Experiment 5 was the result of increased content of intracellular fluid. The former occurred at some degree of hypertonicity before crenation was apparent; the latter at some degree of hypo-

tonicity before lysis took place. This is further evidence in support of the thesis originally stated by Barrett,<sup>1</sup> that cells whose volume is abnormally small in relation to the cell envelope may appear as targets in the stained smear; and suggests that only an increase in this volume is necessary to make them no longer appear so. Target cells whose envelopes are poorly filled in an isotonic medium, namely, the circulating blood, will imbibe more fluid before hemolysing than will the normal erythrocyte. Consequently they can be expected to be more resistant than the latter to hypotonic solutions of sodium chloride. On the other hand, artificial target cells are poorly filled only while in hypertonic solutions, and will resume their original volume-envelope ratio when again placed in an isotonic environment. For this reason, they show no increased resistance to hypotonic solutions of sodium chloride.

The presence of target cells indistinguishable from one another in solutions of relatively varied hypertonicity (Table 3) suggests that cells whose volume-envelope ratio varies in considerable degree can show the same appearance in a stained smear. It seems logical to infer that cells seen as targets in smears made directly from peripheral blood may in a similar manner have considerable variation in their volume-envelope ratios and still appear as targets. Such variations would be accompanied by varying resistance of these erythrocytes to hypotonic solutions of sodium chloride.

**The Significance of the Target Cell.** Target cells after all derive their name solely from their two-dimensional resemblance to a "bull's eye" in the stained film of blood. There is as yet no evidence which enables one to differentiate the target corpuscle of sickle cell anemia from that of thalassemia or from that seen in young and otherwise healthy adults with infectious hepatitis. The latter frequently show no alteration in their erythrocyte counts or hemoglobin values. It is just as logical on the basis of our present knowledge to ascribe fundamental importance to the target cell in one as in the others.

We cannot agree with Bohrod<sup>2</sup> that the target cell is only a young, resistant cell appearing in the blood stream as a response to blood loss. We have recently had the opportunity of observing the blood smears of 2 persons with severe, acquired hemolytic anemias and normal erythrocyte fragility tests. In 1 instance a concomitant reticulocyte count was 82% and in the other 62%. Here there was ample evidence that the bone marrow was pouring large numbers of young cells into the peripheral circulation, yet virtually no target cells were seen. We have seen many similar but less dramatic instances in which there was evidence of blood loss and very active erythropoiesis without increased numbers of target cells in the blood smear.

Dameshek<sup>3</sup> has suggested that the target corpuscle might be the fundamental inherited defect in thalassemia. However, since a cell can assume the form of a target merely by being incompletely filled, it seems illogical to regard such a cell in a smear as fundamentally defective. These corpuscles may be the result of defective formation in the bone marrow or of inadequate supplies of erythrocyte building material, but on the other hand they may enter the blood stream as perfectly normal cells and have their intracellular contents altered by factors

present in the peripheral circulation. It is recognized that the reticulo-erythrocyte may represent a regenerative response to intravascular hemolysis, hemorrhage, or the administration of iron or liver factors to appropriately deficient persons, and is not pathognomonic of any of these. Likewise there are many conceivable mechanisms by which erythrocytes may be poorly filled and appear as target cells in the blood smear. Nevertheless, while we cannot subscribe to such specificity for a corpuscle so widely distributed in a variety of conditions, its prominence in both thalassemia major and minor furnishes food for speculation.

Target cells in large numbers have been often noted in a hypochromic group of anemias and in steatorrhea. The former constitutes in general the group of anemias which respond to iron therapy; the anemia seen in the latter is frequently due to iron deficiency. Thalassemia major and minor belong fundamentally to the group of hypochromic anemias, but differ from other hypochromic anemias in that they remain unaffected regardless of the amount of iron administered. Indeed, according to Wintrobe,<sup>13</sup> they constitute the only hypochromic anemias in which this is true. The prevalence of target cells throughout this group, the close analogy between the blood picture in certain iron deficiency anemias and thalassemia minor, and the unexplained occurrence of large amounts of iron containing pigment in the parenchymal cells of certain viscera in fatal cases of thalassemia major combine to suggest the possibility of some common denominator for the entire group.

It may be that all are, in truth, iron deficiency anemias, and that in some instances the lack of adequate building materials for hemoglobin results in the production of cells whose envelopes are large in proportion of their contents, and which appear as target cells in the blood smear. In the case of thalassemia major and minor, however, lack of available iron may not be due to a depletion of body iron reserves or to an inadequate exogenous iron supply, but rather to the inability of the body to metabolize completely more than a limited amount of iron to hemoglobin regardless of the amount available. The fundamental defect in such a case would be an inherited deficiency of some factor necessary for complete synthesis of hemoglobin from its precursors, the deficiency being quantitatively far more severe in the fatal form of the disease than in its companion, milder, genetically related anemia. It is conceivable that iron converted to the stage of some pigment precursor of hemoglobin, and incapable of being metabolized further, is deposited in certain viscera much as incompletely metabolized products of tyrosine are deposited in cartilage in ochronosis.

The other changes which comprise the striking picture of the child with thalassemia major may be of a secondary and non-specific nature. Erythroblastosis may be the result of the extreme degree of iron deficiency present; the jaundice, which is never marked, may be due to the tendency of abnormally shaped erythrocytes to be more rapidly destroyed than normal erythrocytes, regardless of the cause of the abnormal shape. The changes in the bones are similar to those seen in sickle cell anemia and some cases of familial hemolytic jaundice. These have in common a markedly hyperplastic bone marrow existing continuously from an early date.



This is admittedly speculation but has some theoretical justification. It offers a somewhat more optimistic investigative approach in that the deficient factor may conceivably be found and supplied exogenously. In spite of the long and fruitless search for such a factor, particularly by Whipple and Bradford,<sup>11</sup> it is felt there is reason to continue investigation along this line.

**Summary.** 1. Target cells may be produced *in vitro* by suspending normal erythrocytes in plasma or serum rendered hypertonic either by the addition of chemicals or by evaporation. Severe, rapid dehydration of a dog, with attendant plasma concentration, resulted in a slight but significant increase in the number of target cells in the peripheral circulation.

2. Naturally occurring target cells in a pathologic condition, sickle cell anemia, may be converted to cells of relatively normal appearance by suspending them in the patient's own plasma rendered hypotonic by dilution with distilled water.

3. The target cell is considered to be a cell whose envelope is large in relation to its contents, regardless of the cause of this relationship. Its wide distribution in a hypochromic group of anemias which respond to iron and in the hypochromic anemias of thalassemia major and minor which do not respond to iron suggests the possibility that the latter may be due to iron deficiency. This iron deficiency might be due to some inherited inability to metabolize completely to hemoglobin more than a limited amount of iron.

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### A CASE OF ECZEMA AS A SOURCE OF A STREPTOCOCCAL EPIDEMIC\*

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THIS is a report of an epidemic of streptococcal infection which occurred among nurses working on the Pediatric floor of the Isolation

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Pavilion of the New Haven Hospital during the summer of 1942. Although bacteriologic studies done at the time were incomplete, the clinical and bacteriologic findings pointed to a child with infected eczema as a likely source of the epidemic. The importance which such cases of infected eczema hold in the general pattern of streptococcal infections in childhood has been the subject of a recent report by Boisvert and Powers,<sup>2</sup> and the main purpose of the present paper is to record the circumstances under which a patient with eczema can apparently be instrumental in infecting so many contacts over such a long period of time.

**Case Report.** F. E., a boy of 2, was admitted with a severe streptococcal skin infection. Three days after a normal birth he had developed a vesicular skin disease which eventually became pustular and was treated with ammoniated mercury. After several weeks the skin cleared up. At the age of 8 months, he developed a dry red rash of the popliteal and antecubital fossae. The rash later became vesicular and his temperature rose to 105°. He was given one of the sulfonamides, but this treatment was stopped because a generalized rash appeared which was thought to be due to drug sensitivity. Following this illness, until his admission to the New Haven Hospital 1 year later, the skin had never been clear. Various dietary régimes and local treatments had been tried, but the skin remained moist and cracked and peeled extensively.

In January 1942, the patient was sent to St. Mary's Hospital in Waterbury, Conn., with generalized eczema from head to toe, and an upper respiratory infection. A month later, in February, he was discharged improved, but shortly after returning home the eczema became more active and pustules appeared on his legs and buttocks. This seemed to be helped by tincture of merthiolate, but he became very restless and irritable, and on April 11, 1942, was sent to the New Haven Hospital and admitted to the Isolation Pavilion of the Pediatric Service.

On admission his temperature was normal. His body was covered with a fiery-red eczematous rash. The skin was peeling and there was generalized adenopathy. In the scalp there was a moist crusting lesion and over the face, trunk and extremities, a puffiness of the skin. There were scattered papules over the lower extremities and buttocks. The left external auditory canal was filled with a foul discharge. The drum was not seen. The Kahn test was negative. The urine showed occasional albuminuria and transient W.B.C. The R.B.C. and hemoglobin were normal. The total white count on admission was 48,700 with 53% polys. Total serum proteins were 3.4% but later rose to 6.2%. Serum cholesterol was 165 mg. per 100 cc. and the blood chlorides 109.6 mg. Throat and nose cultures were negative but a Type 14 hemolytic streptococcus was recovered from the skin. Stool examination and a chest Roentgen ray were negative.

The child remained desperately ill for 1 month. Then the course of his illness became one of intermittent remissions and relapses, but with steady improvement. Bouts of fever recurred, generally associated with the appearance of widespread, oozing, pustular lesions from which hemolytic streptococci could be cultured. Whole blood and plasma transfusions were given frequently. Evaporated goat's milk and cane sugar seemed to be the best diet. Carrots, liver, rice, pabulum, lamb, peas, beans and other foods were added slowly, and shortly before discharge he was changed to whole boiled cow's milk.

Of the various therapeutic measures tried, ultraviolet light, sulfathiazole ointment and sulfadiazine by mouth seemed to be the most effective.

He was discharged October 5, 1942, much improved, although his skin was still rough and scaly and slightly erythematous in the intertriginous areas. Cultures of his skin were negative at this time.

On October 29, 1942, he was readmitted. He had gone steadily downhill since discharge. On readmission he had Type 14 hemolytic streptococci in

his nose and throat cultures as well as in cultures taken from his skin. Penicillin soaks were beneficial but had no effect on other bacteria, notably one of the Friedländer group of organisms cultured from his skin. He was put on a Rowe diet, coal-tar ointment and sulfathiazole ointment. As it was the consensus of those who directed his care that his tonsils might be a factor in re-infecting his skin, a tonsillectomy and adenoidectomy were done Jan. 20, 1943. He again improved and on February 6 was discharged. His skin was clearer than it had been since he was 8 months old. There was no oozing, inflammation or pustules. Cultures of his skin were negative at this time.

*Description of Streptococcus Epidemic.* The pediatric floor of the Isolation Pavilion has 2 twelve bed wards on either end of the floor, with 4 single rooms, 2 double rooms and nurses' offices between. Isolation precautions are observed, a clean gown being worn by all those attending each patient. Hands are washed in soap and water and rinsed in lysol solution after visiting a patient. Dishes are steam sterilized.

On June 2, 1942, a house officer who was one of 4 working on the floor became ill with a streptococcal reinfection of an old osteomyelitis sinus tract. On June 3, 2 student nurses came down with scarlet fever. Suspicions were aroused and work was begun in an effort to determine the origin of these infections. There were 20 patients on the floor at the time (4 of whom were or had been ill presumably with streptococcal infections), and as attendants, 27 student nurses, and 2 graduate nurses. All the adults were in good health.

Cultures were taken on June 6 on the 4 pediatric patients with streptococcal disease, but only 1 (F. E.), the child with eczema described above, had a positive culture, the other 3 being convalescent. From F. E.'s scalp, a Group A, Type 14 hemolytic streptococcus was isolated—an organism which had previously been isolated, at the time of his admission. During the next 2 months we cultured the throats of 13 nurses who left the floor with sore throats or scarlet fever, 7 of whom proved to have Group A, Type 14 hemolytic streptococci on immediate typing. The remaining 6 we were unable to type.

It seemed significant to us that F. E. was the only acutely ill child on the floor with a streptococcal infection, and the only one from whom we were able to culture hemolytic streptococci. Because of his restlessness and the severity of his infection he needed constant special nursing care. All student nurses had their turn taking care of him. The bed and the floor beneath the bed were covered with desquamated skin.

The number of student nurses on the floor at any one time varied between 15 and 30. A total of 74 worked on the ward during May, June and July. A few were from the Yale School of Nursing, but most of them were affiliate nurses from other hospitals, arriving in groups of 3 to 12, and remaining from 4 to 6 weeks, depending upon the hospital from which they came.

During the months of June and July, 11 other juvenile patients with streptococcal infections were admitted to the ward. Four were Type 28, 2 Type 26, 2 Type 12 and 1 each of Types 11, 25 and 27. None was on the ward for more than a month except 1 case of osteo-

myelitis, with streptococcal otitis media. He was discharged in 6 weeks.

Subsequent to June 3, 1942, no more cases of scarlet fever developed among the nurses for a few days, but several went off duty with what was called an "upper respiratory infection." Unless epidemiologic studies were being done, probably many of these cases of sore throat among the nurses would not have been studied bacteriologically. The illness was mild, rarely with a temperature over  $100^{\circ}$ , and seldom lasting more than 4 or 5 days. The throat was sore but not striking in appearance, nor was there any extreme degree of malaise and anorexia.

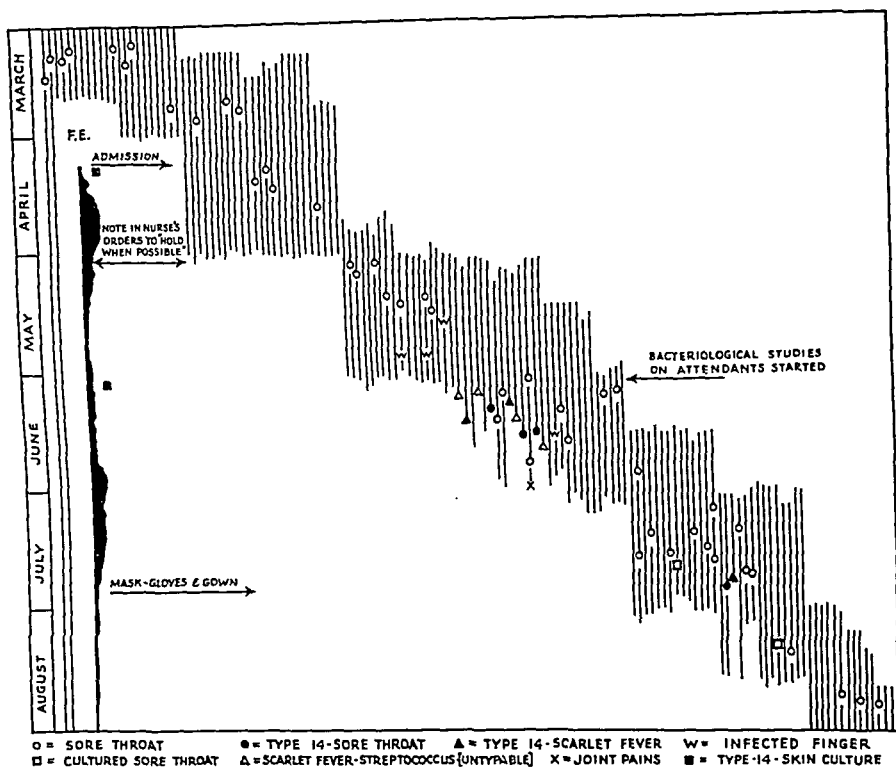


CHART 1.—Relation of F. E.'s fever to nurses' illness. Recorded vertically on the left border of the chart in solid black is the course of F. E.'s temperature and pertinent nurses' orders. Each parallel vertical line (occupying the oblique zone across the chart) represents the duration of each nurse's duty on the ward. The legends on these lines represent the time when they became ill and the character of the illness—see explanation at the bottom of the chart.

As we were able to culture Type 14 streptococci from some of these cases, it seemed that they were part of the same ward epidemic and consequently sickness records of the student nurses before F. E.'s admission were examined to compare the incidence of possible or proven cases of streptococcal disease before his admission with the incidence after his admission.

These data appear in Chart 1. In March and April, before F. E.'s admission, the prevalence of "upper respiratory infections" among the student nurses was 22%. Of 44 nurses, who had been on the floor, 10 had gone off duty with upper respiratory infections. None left for

other illnesses. All of these illnesses had been mild and brief, and no cultures had been taken. During the *epidemic* months of May, June and July, 74 nurses worked on the floor, 37 (50%) of whom became ill with an upper respiratory infection, scarlet fever, or a skin infection. We were not able to take cultures on all these, as some of them were sick in May, before our studies began, and others who became ill after our studies began were affiliate nurses and returned to their own hospital. We were able to culture 13 of the 37, 7 of whom had scarlet fever, and 6 of whom had sore throats.

It is difficult to find a close relationship between the course of F. E.'s illness and the epidemic but as long as he ran some fever the attendants taking care of him became ill. When his infection became less active and after the nurses had begun to wear masks and gloves as well as gowns the epidemic subsided.

We questioned F. E.'s father concerning the health of the family prior to the child's admission to the hospital and learned that 2 aunts and a grandmother had had skin infections of the neck and arms and sore throats after they had begun to help take care of him. His mother who visited him frequently at the hospital came down with scarlet fever in June 1942. We were unable to get throat cultures as she lived in a town some distance away. The patient's father had a streptococcal infection of the nares 6 weeks before F. E.'s admission.

TABLE 1.—TYPING RESULTS IN 14 CASES

		Typing		
		Yale*	RH*	Led.*
	F. E.	14	..	Untypable
	Wlc.	14	Untypable	Untypable
	Lgn.	14	Anti-T 14	Untypable
	Jd.	14	..	Untypable
	He.	14	Anti-T 14'	
	Sdr.	14		
	Hs.	14		
Nurses and interne	Qn.	14		
	Ps.	Untypable	..	Untypable
	Bn.	Untypable	..	
	Js.	Untypable	..	Untypable
	Mr.	Untypable	..	Untypable
	Bly.	Untypable	..	Untypable
	Cld.	Untypable	..	

\* Yale = typing done (early in the epidemic) at Yale University School of Medicine. RH = typing done at Rockefeller Hospital. Led. = typing done at Lederle Laboratories.

**Bacteriologic Studies.** In all, 14 cases of possible streptococcal infection were cultured, from 13 of which Group A organisms were isolated. The other was a Group G organism. Throat swabs were inoculated in beef broth and later streaked on rabbit blood agar plates. Two types of colonies grew out on the plates—one, a typical matt, hemolytic colony, and the other a minute anhemolytic, slightly green colony. Of the 2, the small anhemolytic colony was more common. However, on further subculturing, these would often revert to the typical matt forms. In rabbit blood broth, these organisms produced a greenish hemolysis and fairly granular growth. They were bile-insoluble, and microscopically were typical chain forms.

In Table 1 we have collected data on typing. These data would indicate to us that many of the cultures were somewhat unstable as far as the retention of their type-specific properties was concerned. Of the 13 Group A strains, 7 proved on immediate slide agglutination to be Type 14 and 6 were untypable. Two sets of typing sera were used, one furnished by the Department of Pediatrics, and the other by the Lederle Company. Subsequently, however, when 3 of the "Type 14" strains were checked by Mrs. Rebecca Lancefield of the Rockefeller Institute for Medical Research and by the Lederle Laboratories, they were found untypable. Mrs. Lancefield used the precipitin reaction and the Lederle Laboratories the slide agglutination technique. Because some epidemic strains have been found to contain Type 14 T, but no Type 14 M, Mrs. Lancefield tried to type the 3 strains we sent her with a serum containing Type 14 T antibodies. Two of the strains gave positive agglutinations with this serum.

None of the strains was studied for erythrogenic toxin production.

The results of rabbit immunization done by us as well as by Mrs. Lancefield and the Lederle Laboratories gave inconclusive and irregular results.

**Discussion.** Coburn<sup>3</sup> has called attention to the fact that hemolytic streptococcal infection in infants can acquire a high degree of communicability, and in a recent paper by Boisvert and Powers,<sup>2</sup> attention is called to the possible endogenous source of skin infection in children with eczema and concomitant streptococcal fever. Events described in this paper appear to bear out these observations, and illustrate another point, that secondarily infected eczema in a child can be the source of a veritable epidemic of streptococcosis. As was the case in an epidemic studied by Coburn, we found no evidence of sick nurses transmitting the disease to others, and particularly roommates, during the incubation period. In this respect this epidemic was also centered about its source behaving somewhat as a milk-borne epidemic of streptococcus disease in which groups of new susceptibles are continually being exposed to a heavy "common source" of infection but who fail to pass along the disease to their contacts.

This epidemic also furnishes an illustration of the variegated forms which streptococcus illness may assume, in which about 50% were cases of scarlet fever, 50% sore throats. This, in other words, is an example of the concept of Boisvert and Powers of streptococcosis.<sup>1</sup>

It is noteworthy that in many of the cultures from different patients the strains gave rise to 2 types of colonies, hemolytic and anhemolytic slightly green colonies. Whether this atypical growth can be related in any way to the difficulty encountered in typing the strains, we are not able to say. While the typing sera used by us has not given false positives as far as we know, it is possible that it contains a high titer of antibody against the particular T substance of this epidemic strain. This has not been determined.

**Summary.** A small epidemic of streptococcal diseases among student nurses taking care of a child with secondarily infected eczema is reported. The child was a constant source of Type 14 hemolytic

streptococci for many weeks. During a 3-month period, 50% of the nurses who cared for this child became ill with sore throats or scarlet fever.

We believe that either the "dosage" of the organism put out by this child was high, or that the strain was peculiarly infective.

Difficulty was encountered in typing this epidemic strain, which grew both as a typical matt form, and as a small anhemolytic, slightly greenish colony.

We are indebted to Miss Carol Reynolds for assisting us in obtaining data on the nurses. We are also indebted to Dr. John R. Paul for his guidance and assistance in preparing this paper.

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### THE EFFECT OF SIMULTANEOUS TUBERCULOUS INFECTION ON EXPERIMENTAL TRICHINELLA INFESTATIONS IN GUINEA PIGS

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EVIDENCE suggesting that an unrelated disease process may alter the interpretation of the trichinella skin test was uncovered in the course of investigation on the incidence of trichinosis in North Carolina. In an attempt to determine whether the low incidence of trichinosis in diaphragms obtained at autopsy in this state (2.8%) might be due to light infestations which were undetected after death, a study was made to determine the incidence of positive reactors to skin test antigen.<sup>4</sup> In the course of this study, it was noted that patients with active tuberculosis in 2 sanatoria gave a higher percentage of positive reactions (14.3%) than did those without tuberculosis (7.1%) in 2 general hospitals.<sup>5</sup> Another study was undertaken to determine whether the high incidence of positive skin tests in patients with tuberculosis could be accounted for by unrecognized subclinical institutional epidemics, or if some biologic factor were involved.<sup>3</sup> In order to keep the institutional factor constant, the control non-tuberculous group was chosen from patients confined in hospitals for equivalent periods of time, and was of necessity composed chiefly of psychiatric patients. Because of the unexpected finding that psychiatric patients themselves gave

abnormal responses to skin tests, the experiment could not answer clearly either of the questions.

In an attempt to discover if a true biologic cross-reaction, detectable by skin test, exists between *Mycobacterium tuberculosis* and *Trichinella spiralis*, or if simultaneous infection with both organisms alters the usual course of either infection, the present experiments were undertaken.

**Material.** Thirty-three guinea pigs of approximately 250 to 350 gm. each, obtained from a single source at one time, were divided into 4 groups. Each group was confined in a separate cage. All were fed a standard guinea pig diet of food pellets (Rockland guinea pig diet, vitamin C fortified, Arcady Farms Milling Company, Chicago, Ill.); green vegetables were supplied twice weekly. The animals were kept under standard conditions for 2 weeks before being infected.

The strain of *Trichinella spiralis* used was obtained from the National Institute of Health and was carried in rats. The culture of *M. tuberculosis* (human) Strain C was obtained from Lederle Laboratories and was carried on bean-egg media; the tuberculin (Lederle) (K.O.T.) was made from this strain.

**Methods.** The abdomens of all animals to be tested were shaved. The following skin tests\* were given to all animals 4 days before they were infected: (1) purified protein derivative (P.P.D.) of 0.005 mg. in 0.1 cc.; (2) 0.1 cc. of 1:100 dilution (1 mg.) of tuberculin (K.O.T.) (Lederle); (3) 0.1 cc. of 1:100 dilution (1 mg.) of tuberculin (K.O.T.) (Saranac); (4) 0.05 cc. of 1:10,000 trichinella extract; (5) 0.05 cc. of 1:8000 trichinella extract; (6) 0.05 cc. of buffered saline diluting fluid as a control. The skin tests were read at 20 minutes, 24 and 48 hours. New syringes and needles were obtained for the skin tests and were not used for any other purpose. Each test solution was always given with the same syringe and needle; the syringes and needles were never interchanged. After being used, they were washed with distilled water, placed in marked glass tubes and sterilized in an autoclave.

Group A, consisting of 7 animals, were fed trichinella larvæ, Group B (8 animals) were injected with tubercle bacilli, Group C (9 animals) were fed trichinella larvæ and were injected with tubercle bacilli, and Group D (9 animals) served as controls.

Eight weeks after infection—4 weeks before the animals were sacrificed—the skin tests were repeated, using different sites in the skin of the abdomen.

A rat infected with trichinæ for 8 weeks was killed by a blow on the head; the muscle was dissected away with scissors, ground, and digested at 37° C. for 4 hours in a solution of 0.7% of pepsin and 1% commercial hydrochloric acid. The digested mixture contained 1 to 2 live larvæ per drop. Each animal in Groups A and C were fed 1.5 cc. of this suspension by glass dropper. The mixture was thoroughly agitated between each withdrawal.

One loopful of the culture of tubercle bacilli was emulsified in 5 cc. of sterile saline. On smear this suspension showed 10 to 20 organisms per oil-immersion field; 0.05 cc. was injected into the groin of each animal in Groups B and C on the day following the feeding with trichinæ.

Those animals which had not died were sacrificed 12 weeks after infection and autopsies were performed. Smears were made from the tuberculous lesions in liver, lungs, lymph nodes and spleen and were stained with carbol-fuchsin by the Ziehl-Neelsen technique. The results were recorded according to the Gaffky scale. The entire diaphragm was compressed in a muscle press made of 2 pieces of heavy plate glass and the whole diaphragm examined under a microscope using a 10× objective and 12.5× ocular. If this examination

\* The purified protein derivative (P.P.D.) was furnished by Sharp & Dohme; tuberculin (K.O.T.), trichinella antigen 1:10,000 and diluting fluid by Lederle Laboratories; trichinella antigen 1:8000 by the National Institute of Health. Tuberculin (K.O.T.) was also obtained from Saranac Laboratory.



was negative, approximately 1 to 2 gm. of skeletal muscle from various parts of the body were minced with scissors and similarly examined. The infections were recorded as minimal (1+) if the diaphragm was negative, but larvæ were found in other muscle; mild (2+) if less than 1 larva occurred per field; moderate (3+) if the average was 1 per field; heavy (4+) if 2 or more were seen per field.\*

TABLE 1.—DENSITY OF ORGANISMS IN TISSUE

Animals	Group A Trichinosis		Group B Tuberculosis		Group C Trichinosis and tuberculosis		Group D Control	
	Trichinæ*	Tubercle† bacilli	Trichinæ	Tubercle bacilli	Trichinæ	Tubercle bacilli	Trichinæ	Tubercle bacilli
1	+‡	0	0	+	++++‡¶	+	0	0
2	+	0	0	+	++++	++	0	0
3	+	0	0	+	++++	+	0	0
4	++§	0	0	+	++++	+	0	0
5	++	0	0	++	++++	+	0	0
6	++	0	0	++	++	++	0	0
7	++	0	0	++	++	+	0	0
8	..	..	0	++	++	+	0	0
9	..	..	..	..	++	++	0	0

\* + indicates 0 trichinæ in the diaphragm, but larvæ in other muscle, < 1 gm. ++ indicates < 1 larva per microscopic field ( $\times 125$ ) in muscle press of diaphragm; approximately 1-533/gm. +++ indicates 1 larva per microscopic field ( $\times 125$ ) in muscle press of diaphragm; approximately 400-800/gm. ++++ indicates 2 or more larvæ per microscopic field ( $\times 125$ ) in muscle press of diaphragm; approximately > 800/gm.

† Diaphragm and skeletal muscle negative in muscle press, digestion positive.

‡ Gaffky scale, carbolfuchsin stained smears.

§ Died of streptococcal abscesses.

¶ Died of trichinosis.

**Results.** The preliminary skin tests were all negative. All of the animals injected with tubercle bacilli gave positive tuberculin skin reactions at 48 hours when tested 8 weeks after inoculation; no others reacted. In spite of reports in the literature<sup>1</sup> that guinea pigs will react to trichinella skin test, only 1 animal which was fed trichinæ gave a questionable positive skin reaction to the National Institute of Health antigen; all other reactions to trichinella antigen were negative. One antigen (Lederle) had been used extensively in human beings and found satisfactory. At autopsy, acid-fast tubercle bacilli were demonstrated in smears from the tissues of all animals inoculated with tubercle bacilli. Trichinæ were demonstrated in the diaphragms or skeletal muscles of all animals fed trichinæ. In the control groups the skin tests and examination of tissues were negative.

One animal in Group A died 10 weeks after infection of streptococcus septicemia with generalized abscess formation, but the trichinella infestation was no heavier in this animal than in the remainder of the group. All of the animals in Group B, injected with tubercle bacilli alone, survived for the duration of the experiment. One animal in Group C, infected with both trichinæ and tubercle bacilli, died 10 weeks after infection, apparently with overwhelming trichinosis. The remainder lived for the duration of the experiment.

\* Since there are at this magnification approximately 800 fields in a diaphragm of 1.5 to 2 gm., the number of organisms per gram would be roughly: less than 1 in the minimal infestations (interpreted as 1+), 1-533 in the mild infestations (2+), 400-800 in the moderate infestations (3+), 800 or more, in the heavy infestations (4+).

Each of the 7 animals in Group A, infected with trichinæ alone, had a light (1+) infection at autopsy. In 4 the diaphragm was positive (2+); in 3 the diaphragm was negative, but trichinæ were found in skeletal muscle (1+). In 1 of the latter group (1+) the muscle press preparations were negative, but trichinæ were recovered by digestion. Smears taken from infected areas of the tuberculous animals in Group B were equally divided between those showing Gaffky 1 and those showing Gaffky 2 density of organisms. In Group C the smears of tuberculous lesions showed 6 Gaffky 1 and 3 Gaffky 2 density of organisms; this was comparable to Group B, infected with tubercle bacilli alone.

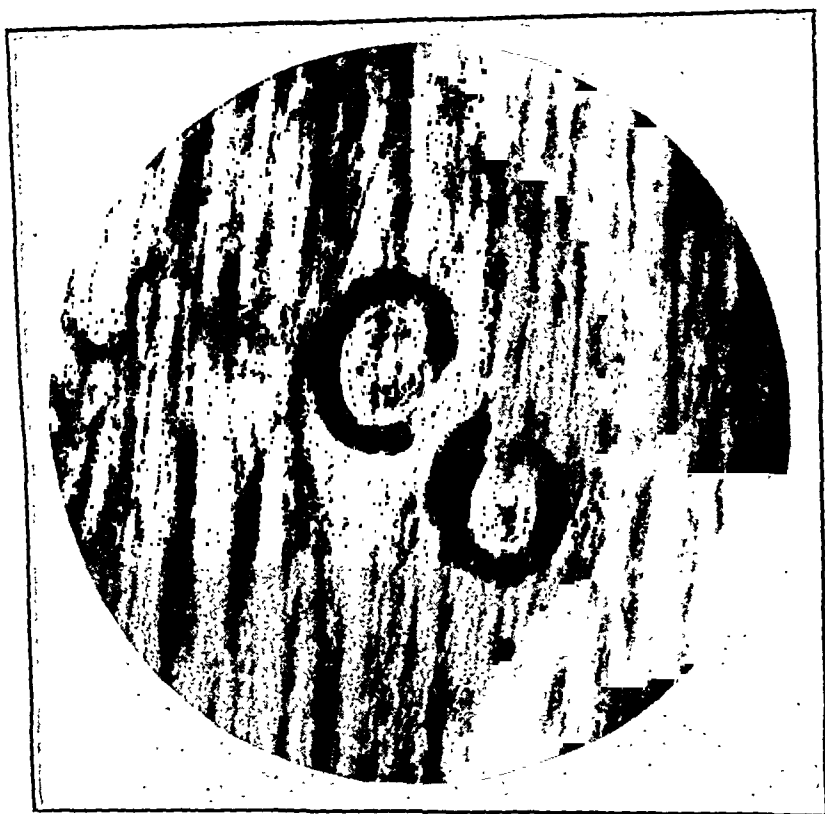


FIG. 1.—Typical field in a muscle press preparation of diaphragm in experimental trichinosis. This density of infection, seen with 10 $\times$  objective and 12.5 $\times$  wide-angle ocular, is the minimum for ++++ density in the table.

The density of trichinella infestation, however, was strikingly increased in most of the animals in Group C; parasites were found easily in each of the diaphragms. Three animals showed mild (2+) infestations comparable to those in Group A; 1 animal showed a moderate (3+) infestation; 5 animals showed a heavy (4+) infestation with trichinæ; this density was not found in any other group.

Treating the data as scored (1, 2, 3, 4+), the mean difference between Groups A and C gives a relative deviate of  $t = 4.02$ , with  $P < 0.01$ . If 1+ and 2+ are grouped as light, 3+ and 4+ as heavy, by the chi square method  $X^2 = 5.666$  and  $P > 0.01 < 0.05$ . By an exact

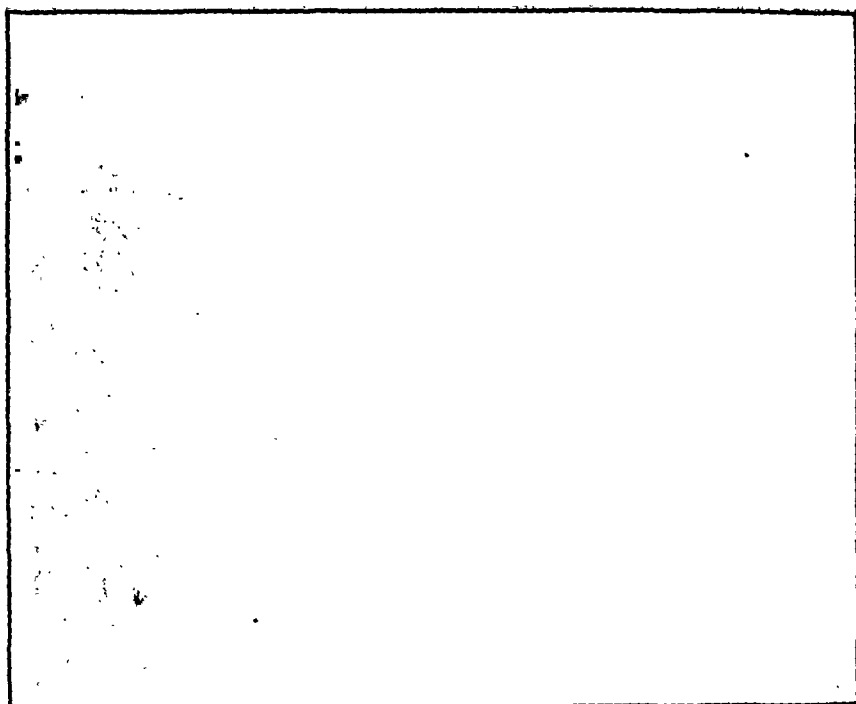


Fig. 2.—Trichinae recovered from digestion of muscle in experimental trichinosis. This density of organisms is comparable to the minimum for ++ density in the table, and is comparable to Group A.

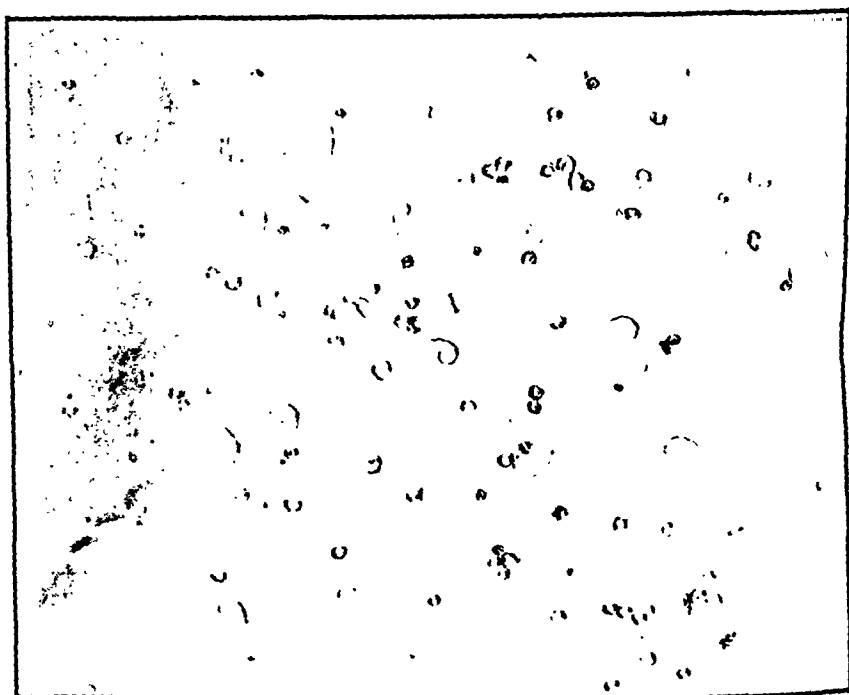


Fig. 3.—Trichinae recovered from digestion of muscle in experimental trichinosis. This density of organisms is comparable to the minimum for ++++ density in the table, and is comparable to Group C.

probability method the same contingency ( $2 \times 2$ ) table gives  $P = 0.03$ . By either of these methods the data are definitely significant.\*

The general health of the pigs in all groups was comparable. Groups A and D gained weight normally and appeared perfectly healthy; Groups B and C gained weight but not to the degree that Groups A and D did. The hair appeared slightly ruffled in each infected group. By clinical observation, it was impossible to differentiate between Group B, infected with tuberculosis alone, and Group C, infected with both trichinosis and tuberculosis.

**Discussion.** The increase in density of trichinella infestation in animals infected simultaneously with trichinae and tubercle bacilli has not previously been described. In some instances the infestation in the diaphragm was up to 1600 times as great as in non-tuberculous animals fed the same dose of larvæ.

Spink, studying the eosinophil response in guinea pigs, injected tubercle bacilli into 1 group of animals and 15 days later fed them trichinous meat. He also fed another group trichinous meat and, after the establishment of eosinophilia, inoculated them with the same quantity of tubercle bacilli used in the previous experiment. No attempt was made to quantitate the inoculum of trichinae. Postmortem examination of stained paraffin sections revealed no differences in the microscopic appearance of either muscle or parasites in the 2 groups of tuberculous trichinous guinea pigs as compared with trichinous guinea pigs. This technique would not allow an estimation of the density of infestation, because of the small amount of tissue on 1 slide.

Spink also studied the effect of killed tubercle bacilli, typhoid vaccine and infections with *Staphylococcus aureus* and *Trypanosoma equiperdum* on the eosinophil count and tissue reaction in trichinous animals.<sup>8</sup> No conclusions can be drawn as to the effect of these organisms on the density of infestation, though differences were noted in the blood picture and tissue response from that in trichinous animals.

It is unlikely that in our experiment either organism assisted directly in the invasion of tissues by the other, since they entered the body by entirely different routes. The trichinae entered through the intestinal tract and the tubercle bacilli by the lymphatics of the groin. It is possible that the tuberculous infection may have entered the blood stream at the same time that the trichinae were being disseminated through the blood, and it may have exerted an influence in this fashion. A tuberculous infection in the anergic state may have an indirect effect on the dissemination of particulate matter, as has been shown with dye in the skin of tuberculous guinea pigs.<sup>6</sup> The only animal to die of trichinosis was in the group simultaneously infected with tuberculosis, but the animal reacted to tuberculin.

In sarcoid, a superimposed tuberculous infection has been said to alter the character of the disease.<sup>7</sup> Secondary infection by the tubercle bacillus is known to occur frequently in tissue damaged by silicosis, sarcoid and Hodgkin's disease; the tubercle bacillus may have an affinity for tissue damaged by infestation with trichinae, but it was not demonstrated by this experiment. If this is true, individuals with

\* We are indebted to Sgt. Charles W. Cotterman for statistical criticism of these data.

trichinosis may develop tuberculosis more easily than patients without the parasitic infestation. This would explain the higher incidence of trichinella skin tests in tuberculous patients.

Does tuberculosis predispose the individual to an infection by a smaller number of trichinae than are required to infect a person without the disease? In the muscle press preparations, trichinae were not found in areas infected by tubercle bacilli, but were discovered in the usual site, though in far heavier numbers than in the non-tuberculous group of animals. That the trichinella infestation had no effect on the tuberculosis is shown by the fact that the density of tubercle bacilli in Group C was no greater than in Group B, infected with tubercle bacilli alone. Under the conditions of the experiment, it is impossible to say whether tuberculous animals can be infected with smaller doses of trichinae than can non-tuberculous animals. The dose used in Group A was small, as shown by the light and mild infestations, but may not have been minimal. If tuberculous patients can become infected with smaller doses of trichinae than non-tuberculous patients, the incidence of positive reactions to trichinella antigen would be greater. Such an explanation would be logical, since most infestations in non-tuberculous patients in this area have been shown at autopsy to be light.<sup>4</sup> Data indicating the minimal degree of trichinella infestation in human beings necessary to produce a positive skin test are not available.

The failure under the conditions of this experiment of the skin of guinea pigs to react to intradermally injected trichinella antigen leaves unanswered the question of possible crossed skin reactivity between *M. tuberculosis* and *T. spiralis*. One antigen (Lederle) had proven satisfactory in our hands in previous human experimentation in the dilution used (1:10,000). The dilution of antigen (1:100) used by Bachman<sup>1</sup> has been thought to give non-specific reactions which can be avoided by a greater dilution;<sup>2</sup> hence, the more dilute solutions were used in this experiment.

**Summary.** Guinea pigs infected simultaneously with *T. spiralis* and *M. tuberculosis*, when sacrificed 12 weeks later, showed heavier infestation with trichinae than did similar animals infected with trichinae alone.

The converse of this statement was not true, since the density of acid-fast organisms found on smears from lesions was no greater than that observed in similar animals infected with *M. tuberculosis* alone.

An increased density of infestation with trichinae in the presence of active tuberculosis may account for the previously reported finding of a higher incidence of positive reactions to trichinella antigen in tuberculous patients confined to sanatoria than in comparable groups confined in general hospitals.

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## CLINICAL ASPECTS OF PAIN IN THE CHEST

## II. PAIN ARISING FROM THE ESOPHAGUS

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DURING the past 2 decades both the medical profession and the lay public have become increasingly aware of the frequency and seriousness of diseases of the coronary arteries. The erroneous assumption is often made by the patient, and occasionally by the physician, that any pain which originates in the substernal or precordial areas—and more especially if it radiates to the left upper extremity—is necessarily due to disease of these vessels. The physician who is particularly interested in cardiac disorders is likely to be concerned only with the question as to whether the pain of a given patient is due to abnormality of the heart, and once he is satisfied that this is not the case often loses interest in the actual cause of the pain. It is not enough to know what does not produce the pain, but one should also know what does produce it. The purpose of this series of studies is to investigate points of differential significance between the various diseases which cause pain in these areas. Especial emphasis is placed on a study of the qualities of the pain, because in some instances the patient's story of the pain offers the only means of diagnosis, and in practically all subjects the history furnishes the essential clue to those further studies which may be needed in order to establish the diagnosis.

The present and succeeding publications deal with disorders of the alimentary tract as causes of chest pain. The frequency of these disorders in causing discomfort in this area of the body is illustrated by the fact that in a series of several hundred patients complaining of this symptom, the cause has been found to be in the alimentary tract in approximately one-sixth of the instances, and in about one-fifth of these the source of the discomfort has been localized in the esophagus. It would appear, therefore, that the esophagus is responsible for 3 to 4% of the instances of chronic or recurrent chest pain.\*

The patients considered in this report were questioned in great detail about their discomfort, and in addition were subjected to com-

\* The apparent frequency of various disorders as a cause of pain in the chest will naturally vary according to the means whereby the cases are selected. Thus, the patients considered in this study were, in the main, individuals who were seen by the author because they were considered—either by themselves or by their physicians—as suffering from cardiac disease. It is likely that physicians especially interested in diseases of the gastro-intestinal tract, or of the lungs, would observe higher and lower respective frequency of esophageal disorders as causes of the thoracic pain. Likewise, the relative incidence of the various types of esophageal disorders varies according to the special interest of the physician. Thus, only 1 patient in the series had carcinoma of the esophagus. Patients with this disorder usually have symptoms of obstruction prior to the development of pain and, hence, are not suspected of having cardiac disease. On the other hand, patients with those disorders of the esophagus which produce relatively little obstruction, but have substernal pain as the presenting symptom, are likely to be seen by the cardiologist.

plete physical examination and various laboratory studies, including gastro-intestinal Roentgen rays, electrocardiograms and other special procedures as seemed indicated. In patients presenting unusual features, an especial attempt was made to reproduce the pain, because this procedure is often of great value in diagnosis.

*Spasm of the Esophagus.* Of the 11 patients with whom this report deals, 8 are believed to have had esophagospasm. One of these presented severe pain and an unusual picture, and will be discussed separately. The other 7 patients had milder symptoms and may be included together. Of these 7 patients, 5 were women and 2 were men. Their ages varied from 30 to 66. The pain was mild and was centered in the substernal region in 5 subjects, and in the precordial region in 2 individuals. There was relatively little radiation. The discomfort was described as burning by 1 patient, and as either a sense of fullness, tightness or squeezing by the remaining 6. The duration varied from a few minutes to several hours. The discomfort was precipitated by swallowing in 4 of the 7 patients, and each of these complained of a feeling of a lump in the chest after swallowing. The esophagus was negative to Roentgen ray examination in all of the patients, none of them being examined at a time when the discomfort was present. Nitroglycerin had a dubious effect in the 2 patients who received it, but all of the subjects obtained partial or complete relief by the use of atropine.

The resemblance of the pain exhibited by these patients to the pain of angina pectoris is noteworthy. This resemblance included the location, the duration and the quality of the pain. However, the precipitating factors were entirely different in that in none of these patients was the pain brought on by exertion, although emotion tended to induce it in 5 of the 7 subjects. The mildness of the pain was of little value in excluding angina pectoris, in that a fairly large percentage of the patients with this disorder complained of pain of minimal severity.<sup>4</sup> The similarity of the pain induced by cardiospasm and that caused by disease of the coronary arteries has been commented on by numerous authors and, indeed, some of them<sup>5,9</sup> have even concluded that the pain of true angina pectoris arose from the esophagus rather than from the heart.

The 8th patient with pain due to spasm of the esophagus presented an entirely different picture.

CASE 1. This 47 year old white male, with a history of rheumatic fever, presented the typical findings of stenosis of the aortic valve, and complained of pain arising in the precordium, radiating to the left shoulder and arm, and brought on by physical exertion and by emotion. This pain was relieved by nitroglycerin. In addition he had another and entirely different pain, which was localized to the lower retrosternal region, which lasted from 1 hour to as long as 2 days, and was usually constricting but sometimes stabbing in quality. This pain was quite severe, being somewhat more violent than the anginal attacks. During this second type of pain he often had difficulty in swallowing and a feeling that something was hanging in the region of the lower third of the sternum. At times the difficulty in swallowing, which usually accompanied the pain, was so great that fluids would regurgitate through the nose

when he attempted to swallow during the attacks. He had noted that these seizures of substernal pain were sometimes precipitated by straining at stool, and were frequently induced by the ingestion of alcoholic beverages. His pain was usually aggravated by deep breathing, but holding the breath did not give complete relief. The termination of his attacks was remarkable. This came suddenly and was associated with a sound which could be heard not only by himself but by others, and which was described as gurgling in character, the sound seeming to arise in the lower sternal region. Immediately following this he felt as though something were "turned loose," and had a warm dripping sensation, internally. Because of the frequency and severity of these attacks of pain the patient had become addicted to morphine.

Physical examination was negative except for the presence of an enlarged heart and of aortic stenosis. Radiologic examination at a time when he was free of pain was negative. When repeated during an attack of pain, marked obstruction was found at the lower end of the esophagus, the appearance being typical of cardiospasm. At a time when he was free from pain a stomach tube was introduced and the stomach was inflated with air. This caused a typical seizure of pain. The following day, after thorough atropinization, the procedure was repeated and three times as much air had to be introduced into the stomach in order to cause the pain as before. The patient obtained marked relief by the use of antispasmodics, but continued to have his pain in milder form when he became emotionally disturbed.

This patient resembles, in many respects, the individual reported by Eideken.<sup>3</sup> His subject, a man of 67, likewise had aortic stenosis. He had pain induced by effort and also pain brought on by swallowing. The former was benefited by nitroglycerin, the latter by belladonna and hyoseyamus. The distribution of the anginal pain and the pain of esophageal origin was apparently identical. Wolferth and Eideken<sup>10</sup> pointed out the frequency with which spasm of the esophagus simulated angina pectoris, and believed that esophagospasm constituted the most frequent condition which led to difficulties in differential diagnosis. They studied a large series of patients with substernal pain, and pointed out that while spasm of the esophagus is often painless, there are some instances in which the discomfort may be very severe. They emphasized the point,—well borne out in the case cited above—that it is often necessary to carry out radiologic examinations during the pain in order to detect the esophagospasm.

The chief points which serve to differentiate pain due to esophagospasm from that due to angina pectoris are: (1) the lack of relationship to effort; (2) the frequent relationship to swallowing; (3) the less striking relief from nitrites; (4) the beneficial effect of atropine; (5) the tendency toward longer duration (the pain of angina pectoris does not ordinarily last more than a few minutes<sup>4</sup>); (6) the lack of electrocardiographic changes during the pain; and (7) the demonstration of spasm of the esophagus by radiologic or esophagoscopic examination.

*Discomfort Due to the Trapping of an Air Bubble in the Esophagus.* CASE 2. A male, aged 52, with a minimal rheumatic mitral lesion and a healed duodenal ulcer, complained of mild substernal discomfort without radiation, lasting for a few seconds. His discomfort consisted of a feeling of fullness and this was quickly followed by a vibratory sensation which he described as feeling "like the nozzle of a garden hose were squirting in the chest." On examination there was a Grade 2 systolic blow at the apex and a faint presystolic murmur when he lay on his left side. At times both heart sounds in the region of the



sternum had a high-pitched, metallic quality. This phenomenon varied with position and at times was not present. Fluoroscopic examination of the esophagus showed that he had a large gas bubble in the stomach and that pressure in the epigastrium forced part of the gas up into the esophagus, where the bubble tended to land. At this time the metallic quality of the heart sounds reappeared, such quality evidently being due to the beating of the heart on the gas bubble. When a stomach tube was passed and the stomach inflated the patient's sensation was not reproduced. However, when the tube was withdrawn into the lower esophagus and air was suddenly run into the tube with a syringe, he perceived a sensation something like the one of which he had complained. When the air in the syringe was mixed with water and the mixture was suddenly forced through the tube into the esophagus the patient stated that the sensation was exactly reproduced.

In this patient, as in so many others, the chief concern was not with the discomfort, which was very mild, but with the patient's interpretation of the significance of the discomfort. Knowing that he had heart disease he was inclined to attribute the curious substernal sensation to a serious cause. When the sensation was reproduced and its mechanism explained, all his anxiety disappeared.

*Congestion of the Esophagus as a Cause of Discomfort.* CASE 3. A male, aged 50, stated that for 6 months he had had a mild sensation of fullness and tightness in the lower part of the throat. This sensation would come on about 5 seconds after he lay down, would remain while he was in the recumbent posture, and would disappear within a few seconds after he sat up. He had no discomfort on swallowing. Because a relative had recently died from angina pectoris and had had most of his pain in his neck in the midline, the patient was concerned about the possibility of having angina pectoris. Physical examination, electrocardiograms and radiologic study of the esophagus were negative. The story of the curious relationship to posture suggested that increased venous pressure in the esophagus might be concerned with the discomfort. Therefore, when he was in the standing position, in which he had never had the sensation, pressure was exerted about the lower part of the neck and the sensation in the throat was exactly reproduced. Release of the pressure caused it to disappear. Repetition of the procedure when the patient was recumbent caused aggravation of the preëxisting discomfort. Lowering of the head also aggravated the sensation. With the patient in the recumbent position sudden pressure on the abdomen aggravated the sensation. When he was sitting up and entirely free of the discomfort, the same procedure produced it in milder degree. He was told that his discomfort was probably the result of congestion of the esophagus and was advised to be esophagoscoped in order that one might know whether or not varices were present, but he was completely satisfied with the explanation and declined esophagoscopy. Nevertheless, it seems probable that congestion, either with or without large varices at the upper end of the esophagus, was responsible for the rather bizarre symptoms of which he complained.

Insofar as I am aware, discomfort of this type complained of by the patient just described has not been heretofore mentioned in the literature.

*Carcinoma of the Esophagus.* CASE 4. A man, aged 67, had noted dysphagia without pain for 4 months, and slight pain behind the xiphoid, radiating to the lower substernal region and to the epigastrium, for 3 weeks. The pain was both burning and squeezing in character, was constantly present, and was increased by swallowing, particularly solid food. Physical examination was negative as was the Roentgen ray of the esophagus. However, esophagoscopy revealed a fungating mass which was proved by biopsy to be a carcinoma.

This patient illustrates the fact that carcinoma may be undetectable except by the esophagoscopic method.

**Discussion.** As the result of the cases mentioned and of those described by others, certain generalization may be offered concerning chest pain induced by disorders of the esophagus.

Disorders of the esophagus are frequently painless, but in some instances the pain may be of great severity.

Dysphagia is usually present but is absent in many cases. This is particularly true in patients who have peptic ulcer of the esophagus, either with or without esophageal hiatal hernia.<sup>1,2</sup> In such patients pain is an early symptom, while difficulty in swallowing appears late. The reverse is usually the case in subjects with esophagospasm, and in those with carcinoma.

Esophageal pain is likely to consist of a feeling of burning<sup>6</sup> or of fullness, distention or constriction.

The most common location for esophageal pain is the lower substernal region and it not infrequently radiates to the epigastrium, or to the region of the dorsal spine. However, as was pointed out by Moersch and Miller,<sup>8</sup> the pain may be very widespread, may radiate to the ear, to the face, or more commonly to the neck, shoulder, arm and hand. According to the same authors, pain in the forearm and hand is likely to be localized in the radial rather than in the ulnar side. The point may be of some differential diagnostic value with respect to angina pectoris.

The duration of the individual attacks of esophageal pain is very variable. At times the discomfort lasts only a few seconds, while in other instances it endures for weeks.

Among the factors which may precipitate esophageal pain are *swallowing*, which is especially important in patients with spasm, with carcinoma, and in individuals with obstruction due to stricture or to scar tissue as the result of scleroderma; *eating*, which is especially important in patients with peptic ulcer of the esophagus; the *recumbent position*, which is most likely to precipitate the pain in patients with esophageal ulcer (the regurgitation of acid into the ulcerated area is favored by the recumbent posture); the ingestion of *highly seasoned food* and of *alcoholic beverages*, which is likewise especially important in patients with peptic ulcer of the esophagus; and especially the act of *swallowing when the patient is lying down* (here gravity does not aid the descent of the food and any lesion which interferes with peristaltic waves tends to allow food to be trapped when the patient is in the recumbent posture).

Among the factors which tend to alleviate esophageal discomfort are *antispasmodics*—those of the atropine group being the most beneficial; and the assumption of the upright position. The latter factor is especially important in patients with peptic ulcer of the esophagus associated with congenital shortening of this organ and with hiatal hernia. Some patients with this syndrome need to have the head of the bed elevated, because only in this way can the regurgitation of the acid contents from the stomach onto the ulcerated area be prevented.

The character of the pain in the patients reported was sometimes constrictive and sometimes burning. This is in keeping with the observations of Jones,<sup>7</sup> who found that in certain normal subjects burning pain (analogous to "heart burn") was produced by distention of a balloon in the lower esophagus. In other individuals the discomfort consisted of a feeling of pressure. Since the pain of angina pectoris may also be either constrictive or burning,<sup>4</sup> it is evident that the character of the pain is of limited value in differential diagnosis between these two conditions.

The tendency of pain arising from the esophagus to resemble in distribution that arising from the heart, was likewise elucidated by the work of Jones.<sup>7</sup> He noted in healthy persons that the pain produced by distending the esophagus sometimes radiated from the substernal area to the tip of the left shoulder and down the left arm. Furthermore, he observed that distention of the esophagus still caused pain after all of the thoracic sympathetic ganglia had been removed, and concluded that either pain fibers from the esophagus were carried in the vagi, or that some of the fibers passed up the esophagus and entered the cord in the cervical region. Jones pointed out the importance of the factor of summation of afferent impulses from different localities in determining the localization of esophageal pain. Thus, in 1 of his patients the removal of a cervical rib abolished the radiation of the pain to the left shoulder and arm but did not abolish the substernal distress. Similarly, it is possible that the coexistence of angina pectoris may increase the likelihood of radiation of esophageal pain to the left shoulder and arm, as in the case reported by Eideken, and in the case cited in this communication.

**Summary.** A series of patients with pain arising in the esophagus and simulating, in some degree, that due to disease of the heart has been presented. One of the patients had both angina pectoris and severe pain due to spasm of the cardiac end of the esophagus.

The location, quality and intensity of the pain due to esophageal disorders may be indistinguishable from that due to disease of the coronary arteries. In both conditions the pain may be precipitated by emotional disturbances and by the ingestion of large quantities of food.

In the differentiation of angina pectoris from pain brought about by disorders of the esophagus the following points are of value.

1. Pain arising from the esophagus is not ordinarily related to muscular exertion.

2. Pain precipitated by swallowing or coming on during eating is likely to be due to esophageal disorders. The ingestion of highly seasoned food or of alcoholic beverages is especially apt to precipitate esophageal pain.

3. The presence of even a minor degree of dysphagia constitutes strong evidence in favor of esophageal pain.

4. The duration of esophageal pain is more variable (a few seconds to many hours) than is that of angina pectoris, which usually lasts for a few minutes.

5. Electrocardiographic, radiologic and esophagoscopic studies are

of great value when they yield positive results, but many errors are made by placing undue emphasis on borderline findings.

6. Atropine and allied drugs often produce striking relief in patients with esophageal pain but do not usually affect anginal pain. Nitroglycerin may relieve esophageal pain but the effect is rarely as striking as in anginal pain.

7. Fluoroscopic study of the esophagus, made while the pain is present, may yield positive results when the same procedure is quite negative, if carried out in the pain-free state.

8. One of the most useful methods of diagnosis is induction of the pain when the patient is under observation. This can nearly always be done by muscular exertion in patients with angina pectoris. Esophageal pain can be precipitated in some patients by the ingestion of highly seasoned food or of alcoholic liquors, and especially if these irritants are swallowed when the patient is recumbent. In other patients esophageal discomfort may be induced by distending the stomach or the esophagus with air or with water. Since these procedures may cause discomfort in healthy persons they are only significant when they reproduce exactly the spontaneous discomfort of which the patient complains.

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## CLINICAL ASPECTS OF PAIN IN THE CHEST

### III. PAIN ARISING FROM THE STOMACH

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ALTHOUGH the importance of disorders of the stomach and cardiac end of the esophagus as causes of mild distress localized in the lower substernal area is well known, comparatively little attention has been

paid to the significance of such disorders as causes of widespread and severe pain resembling in character and in distribution that often induced by diseases of the coronary arteries. The recent study by Balchum and Weaver<sup>1</sup> in dogs indicated that the sensory nerves of the stomach are derived in the main from the lower dorsal segments but that branches may come from as high as the fourth dorsal level. These observations would account for the occurrence of pain in the middle of the chest. However, the observations of von Bergmann,<sup>3</sup> Jones,<sup>13</sup> and others, as well as those to be reported in the present study, indicate clearly that pain produced by disorders of the stomach may be felt in the upper chest, neck, shoulder and arm, the left side of the body being involved more frequently than the right. Whether pain of this distribution is transmitted by nerves from the stomach itself, or by pathways from contiguous structures—such as the diaphragm, esophagus and heart—need not be considered in this communication, which is not concerned with the route of transmission but rather with the qualities of the pain and with the criteria whereby it may be differentiated from that due to disease of the coronary arteries.

The patients to be discussed represent a selected group. They were seen by the author because they were considered, either by themselves or by their physicians, to be suffering from pain arising in the heart. The majority of patients with gastric disturbances have their discomfort in the upper abdomen and are not likely to present themselves as "heart cases." However, since it is in the exceptional patient, with pain referred to the chest, that confusion is apt to arise, it seems worthwhile to report such a group of selected cases even though they do not present the typical symptoms of their underlying gastric disorders.

*"Functional" Distention of the Stomach as a Cause of Pain in the Chest.* Under this general category may be grouped the patients in whom the pain seems to be related either to aerophagia, to pylorospasm, or to an unusually low position of the stomach. Since these conditions frequently occur together they need not be discussed separately.

Of the 13 patients in this group, 9 were females. The ages ranged from 30 to 68.

The chief sites of *location* of the pain were in the left lower chest, anteriorly, below the cardiac region (7 patients), and in the precordial area (4 subjects). The remaining 2 patients complained of pain behind the lower sternum. The discomfort radiated to the left shoulder in 3 subjects, to the left arm in 2, and to the back of the chest in 4.

The *duration* of discomfort was variable but most of the patients stated that it lasted more than an hour. The *severity* varied from minimal to moderate and no patient complained of marked distress. Most of them were concerned about the possible significance of the pain rather than about the discomfort itself. The pain consisted of a feeling of fullness, tightness or pressure in 8 subjects, was of burning character in 2, stabbing or shooting in 2, and aching in 1 instance.

The pain was related to posture in 6 subjects, being aggravated by

lying on the left side in 4 patients, was worse on the right side in 1 person and was increased by the upright position in another.

Eleven patients stated that the pain bore no relation to exertion. Two patients gave a history of pain made worse by walking or by other bodily effort. Both of these subjects were subjected to severe exertion under observation and in neither instance did the pain develop.

The relationship of the pain to digestive functions was striking and was the most important feature in the history. Nine of the 13 patients obtained complete relief by belching. Two obtained partial relief and 2 were not affected by this act. Four subjects had noted that expulsion of the flatus gave partial to complete relief from the discomfort, and 3 patients had obtained relief from pain by vomiting. Eating aggravated or precipitated the pain in 4 subjects but produced relief in 1. Two subjects complained of some pain caused by swallowing and it is probable they had cardiospasm in addition to pylorospasm.

There were 3 patients who stated that the pain was definitely aggravated by deep breathing or by cough, and in 2 of these coughing under observation did cause mild pain. These patients were thought at first to have discomfort of pleural origin, but further studies showed that in spite of the relation to breathing and the lancinating character of the pain, the discomfort was arising from the stomach.

Emotional disturbances tended to induce the pain in 6 of the patients. Mild to severe anxiety states were observed in 10 of the 13 subjects, 9 individuals being frightened about the possibility of cardiac disease, and the tenth having cancerophobia. In 7 of the patients the attacks of pain tended to be associated with palpitation.

Positive findings on physical examination were conspicuously absent in this series of patients. Attempts to reproduce the pain by abdominal pressure was successful in only 2 instances, and 4 other patients had minimal to moderate tenderness in the epigastrium.

The results of radiologic examination were likewise not impressive. Pylorospasm could be demonstrated in 5 subjects. Two patients displayed an unusual degree of ptosis of the stomach. One exhibited regurgitation of the barium meal into the esophagus. In the remaining subjects fluoroscopic examination yielded entirely negative results.

Normal electrocardiograms were encountered in 10 patients, 2 subjects displayed frequent ventricular premature beats, and the remaining individual had well-marked inversion of the T waves in the fourth lead. This patient had been incorrectly diagnosed as having angina pectoris, and since his case is fairly typical of the syndrome as it occurs in the older age group it may be summarized here:

A 60 year old male complained of mild discomfort in the region of the left lower anterior part of the chest. The pain lasted from a few minutes to several hours and usually radiated to the left shoulder. It consisted of a feeling of tightness or of fullness, and had been present for about 2 months. When asked about the relationship of the pain to effort he at first stated that it was likely to come on during exertion. It was likewise aggravated by eating large meals but tended to be relieved completely either by belching or by expulsion of flatus. Physical examination revealed questionable cardiac enlargement and slight hypertension, the systolic and diastolic pressures being

170 and 105 mm. of mercury, respectively. There was slight slurring of the QRS complexes in Leads 2 and 3, and  $T_1$  was inverted. The heart was slightly enlarged by Roentgen ray and fluoroscopic examination of the stomach yielded negative results. He had been told that he had angina pectoris and had developed an anxiety state in regard to his heart.

The story that the pain frequently endured for more than 1 hour and that it was so strikingly relieved by belching, plus the observation that the patient tended to swallow air, led to further investigation. On repeated careful questioning he stated that he was not certain whether or not the pain was related to effort but felt quite sure that it tended to come on after a heavy meal. When he climbed stairs under observation (200 steps in 10 minutes) he became very fatigued but had no pain whatsoever. An electrocardiogram taken immediately after the exercise revealed that the previously inverted  $T_1$  had now become upright. When a tube was passed and 1500 cc. of air were slowly introduced into the stomach a feeling of discomfort identical with that which occurred during his spontaneous attacks was induced.

*Comment.* In this patient the presence of hypertension and of slight cardiac enlargement, plus a hastily taken initial history and overemphasis on the importance of electrocardiographic changes, led to a false diagnosis of angina pectoris, when actually the patient's discomfort was due to a much more benign disorder.

As illustrated in the patient just cited, the reproduction of the pain is at times a valuable procedure in diagnosis. Eight patients in the group were tested in this manner by having their stomachs inflated. Obviously, the introduction of sufficient air or water into the stomach will cause discomfort in anyone. The point of the test was not whether some discomfort was produced but whether discomfort simulating exactly that which the patient experienced during the spontaneous attacks could be induced by this procedure. In 6 of the 8 subjects the inflation of the stomach with air yielded a positive result in the sense of causing pain similar to that of which the patient originally complained. In 1 patient the introduction of air induced discomfort somewhat like that of the spontaneous pain but the patient was uncertain until the air had been withdrawn and 2000 cc. of water was introduced in the tube. She then felt sure that her pain had been reproduced. In the remaining subject these procedures induced discomfort which was quite unlike that which brought the patient to the physician.

The effect of atropine on the pain was studied under observation in the hospital in 7 of the 13 subjects. Five patients obtained either complete or practically complete relief. The remaining 2 subjects were not affected.

As an example of a patient illustrating most of the features of the syndrome of chest pain due to distention of the stomach, the following subject may be cited:

A 36 year old female had suffered for 2 years from attacks of mild burning and aching pain in the left lower chest anteriorly, and also in the lower sub-sternal region. The attacks lasted only a few minutes and usually began at night, especially when she was lying on the left side. The pain was partially or completely relieved by turning on the right side, but was increased in intensity by sitting up or by standing. During most of the attacks of pain she was conscious of pounding and skipping of her heart. Her discomfort was sometimes benefited by drinking cold water, by eating a small amount of food, by the ingestion of soda, or by the expulsion of flatus, while belching

gave complete relief. One of her cousins had had cardiac disease and the patient was afraid that she herself had developed it, and displayed a mild anxiety reaction. The physical examination was negative except for her slender habitus. She was 5 feet 7 inches tall and weighed 101 pounds. Electrocardiograms revealed no abnormality. Fluoroscopic examination of the stomach showed that this organ was very ptotic and emptied more readily with the patient lying on the right side than when she lay on her back or on the left side. When a tube was introduced and the stomach inflated either with water or with air, ventricular premature beats set in and she developed her typical pain. Under observation the pain was aggravated by lying on the left side, or by sitting, and was improved by turning on the right side. Her physical discomfort was completely alleviated by atropine and her anxiety by assurance.

*Comment.* This patient evidently had some trouble in emptying her stomach either in the upright position or when she lay on the left side, because it occupied a very low position, and in these postures the pylorus was well above the dependent part of the greater curvature. Her discomfort was referred to the chest and thus led to an anxiety state because of fear concerning cardiac disease which did not exist.

The chief clinical manifestations exhibited by patients who have chest pain as the result of gastric distention due to functional disorders may be summarized as follows: In most instances pylorospasm, aerophagia, gastroptosis or a combination of these minor disturbances is present. Although the patient may be of either sex and of any age, most of the individuals with this syndrome are middle-aged females. Anxiety and palpitation are commonly associated symptoms. The discomfort often sets in when the patient is lying on the left side and it usually consists of a feeling of fullness which is likely to be located in the left lower chest, anteriorly, but which may have the typical distribution of pain due to coronary disease. The duration is more variable and is often longer than in the case of attacks of angina pectoris. The pain is usually mild but this fact is of little differential value because pain due to coronary disease is likewise frequently mild. Emotional disturbances and eating often induce the discomfort, which may be relieved by expulsion of flatus, or by vomiting. However, the act of belching and the administration of atropine produce the most striking benefit. The reproduction of the pain as to location, quality, and so forth, by inflation of the stomach, is a valuable diagnostic aid. Pain due to this cause may be stabbing in character and aggravated by breathing, and may therefore offer a superficial resemblance to that due to disorders of the pleura.

*Esophageal Hiatal Hernia.* Following von Bergmann's<sup>3</sup> studies on the frequency and the importance of this condition as a cause of pain in the chest the clinical manifestations have been discussed by a number of authors<sup>7,14,17,19,25</sup> and more particularly by Jones,<sup>13</sup> who reviewed the symptomatology in 128 cases. He discussed in detail the points of similarity between pain due to coronary disease and that due to hiatal hernia, and pointed out that the smaller herniæ were more likely than the larger ones to produce pain resembling that of angina pectoris. Recently Schnepf<sup>24</sup> has emphasized the importance of hiatal hernia as a cause of pain behind the lower sternum ("heart burn") during the last trimester of pregnancy.



Of the 24 patients in the present series with thoracic pain due to disorders of the stomach, 4 had esophageal hiatal herniæ. The symptoms in these patients were very similar to those described by Jones,<sup>13</sup> the pain being felt in the substernal region or the lower left anterior chest and radiating to the left shoulder or to both shoulders. The duration of the discomfort was very variable, lasting from a few minutes to as long as 3 days. The pain was mild to moderately severe and consisted of a sense of fullness or constriction. Two of the 4 patients stated that the distress was precipitated by the recumbent posture. All of them noticed aggravation following large meals, and were sometimes relieved by belching. One patient obtained relief by alkalis. (This led to the suspicion of an ulcer either in the hernial sac or in the esophagus but this could not be demonstrated by Roentgen ray and esophagoscopy examination was not done.) There was a tendency for the pain to be aggravated by emotion and by alcoholic liquors. One of the 4 patients also had typical angina pectoris on effort with a slight difference in the distribution and quality of the pain and with relief by nitroglycerin. The pain due to the hiatal hernia was not affected by nitroglycerin.

The only patient in the series presenting symptoms strikingly different from those observed in many of the cases reported in the literature was an individual who apparently developed a perforation of the hernia.

A 57 year old man had had occasional mild sensations of distention and fullness in the left lower anterior chest below the precordium for about 15 years. This usually followed large meals and was relieved by belching. Three weeks before admission to the hospital the attacks began to increase in frequency, intensity and duration. A few days later he noted that in addition to his previous distress he was having a sharp stabbing pain beginning in the same general region but radiating to both shoulders and markedly aggravated by deep inspiration, coughing or sneezing. About the same time he began to have fever and irregular chills and developed an increasing leukocytosis. Physical examination was essentially negative and electrocardiograms showed no significant changes. Fluoroscopic study revealed a small esophageal hiatal hernia and upward displacement of the right side of the diaphragm. It was believed that he had a subphrenic abscess and operation was advised. This was refused and after a stormy course he gradually recovered following symptomatic treatment and the use of sulfonamide drugs.

*Comment.* It seems highly probable, although unproven, that this man had a perforation of an esophageal hiatal hernia, leading to a subphrenic abscess.

*Cascade Deformity of the Stomach.* This disorder resembles hiatal hernia in that it is a frequent finding in patients who have no symptoms. The typical deformity which was first described by Rieder<sup>21</sup> in 1910 tends to occur intermittently and may be observed to disappear during fluoroscopic examination. The upper pouch is usually situated posteriorly but may be located either to the right or left of the body of the stomach. Hence, the pain when present is likely to be related to position, because drainage of the abnormal pouch usually occurs better in one posture than in another. The discomfort is likely to be completely or partially relieved by lying down. In most of the patients the optimal position is lying on the left side,<sup>6,26</sup> but in some patients

comfort is best achieved by the right lateral posture—as in the case described below—or by the prone position.<sup>21</sup>

The cascade deformity of the stomach usually produces no symptoms. When pain occurs it is usually situated in the left hypochondrium or the epigastrium, as in the cases cited by Upham,<sup>26</sup> by Brown and McHardy,<sup>6</sup> and by Rendich and Connors.<sup>22</sup> The latter authors mention palpitation as a common symptom but little attention has been paid to the fact that in exceptional instances the pain may be localized in the chest and may resemble closely the discomfort produced by diseases of the coronary arteries. Retrosternal pain in 1 patient was described by Schaffner and Burton,<sup>23</sup> while Kaufman<sup>16</sup> and Harrison<sup>11</sup> have described patients with pain in the chest resembling that produced by cardiac disease.

Among the factors which may precipitate pain certain positions, and more particularly the standing or sitting postures, have been mentioned. Other precipitating factors which are operative in certain cases are rapid eating (case of Schaffner and Burton<sup>23</sup>) and swallowing (case cited below). Among the alleviating factors are belching, the expulsion of flatus, bowel movements, and one or the other of the recumbent postures. The relief experienced by measures which empty the large bowel can probably be ascribed to the importance of pressure from a distended splenic flexure in producing the cascade deformity.<sup>8,21</sup> One interesting feature of the condition is that the deformity may be noted when a small amount of barium is swallowed and then disappear when additional barium is ingested and the stomach becomes filled<sup>8</sup> and that, similarly, the pain has a tendency to come on after small amounts of food, and may disappear when additional food is taken.<sup>21</sup>

I have observed 3 patients with pain in the chest due to cascade deformity of the stomach. One of them has been reported elsewhere.<sup>11</sup> The 3 patients were all males addicted to overindulgence in alcoholic beverages. The pain was felt in any part of the left anterior chest and radiated to the left arm. It endured from a few minutes to 2 hours with a distinct tendency toward periods of aggravation lasting from a few seconds to a minute, followed by periods of relative freedom from discomfort of a minute or more. The intensity varied from mild to extremely severe. The pain was cramping in character and tended to be precipitated by bending forward or by lying on the side. Turning to the opposite side produced partial but not complete relief. One of the 3 patients had mild burning pain on swallowing, but the other 2 did not. All of the 3 subjects were emotionally unstable and heavy drinkers, the ingestion of alcoholic liquors tending to precipitate attacks of pain. Of the 3 patients, the 1 presenting the most puzzling and dramatic clinical picture was the following:

A white male, aged 58, had indulged heavily in alcoholic beverages for a number of years. Recently he had abandoned whisky but had taken large quantities of beer, averaging 10 to 20 bottles per day. Ten years before he had had symptoms suggestive of peptic ulcer and a deformity of the lesser curvature of the stomach just above the pylorus had been demonstrated by fluoroscopic examination. He was first seen by the author in a state of mild

congestive failure which rapidly subsided on treatment. At this time a story of mild aching pain in the precordial region and left arm, induced by walking and lasting only a few minutes, was obtained. The heart was slightly enlarged; the systolic and diastolic blood pressures were 170 and 102 mm. of mercury, respectively. Electrocardiogram revealed only left axis deviation with low voltage of  $T_2$  and  $T_3$ . Under observation walking a distance of 200 yards produced the discomfort in the chest and arm. The same exertion undertaken at the same rate 2 minutes after the sublingual administration of nitroglycerin caused no discomfort.

Three months later he began to have violent attacks of "squeezing" pain radiating from the substernal and precordial regions to the left pectoral area, and into the left shoulder and arm. These attacks would last from 1 to 3 hours. Paroxysms enduring for about a minute, during which the pain was violent, were separated by 1 or 2 minutes of partial relief. Large doses of opiates were required, and even then he did not obtain complete relief. At times he noted that swallowing caused a mild burning retrosternal pain in the midsternal region. Physical examination revealed moderate cardiac enlargement and slight hypertension, with a tendency for the blood pressure to rise during the paroxysms of pain. Electrocardiograms were taken both during and between attacks and revealed only left axis deviation and isoelectric T waves in the second and third leads. The records taken during the attacks showed no significant difference from those taken when he was free of pain. During the first 4 weeks of illness the body temperature varied from 100 to 101° F., and the leukocyte count ranged from 7000 to 14,000.

The patient was at first thought to have myocardial infarction but as the illness continued with almost daily repeated paroxysms of pain, further investigations were made. Fluoroscopic examination carried out when the pain was absent revealed a typical cascade deformity of the stomach. The barium passed freely through the esophagus into a fundic pouch. Only when this pouch was filled did the barium spill over into the body of the stomach.

On the following day fluoroscopy during a seizure of pain showed obstruction of the distal end of the esophagus and the barium slowly trickled through the cardia into the main portion of the stomach. The fundic pouch could not be visualized in any position. Apparently there was torsion of the portion connecting this sac to the remainder of the organ.

Following this observation the patient was given frequent feedings of a bland diet and large doses of antispasmodic drugs. The pain was practically completely relieved within 48 hours and no further paroxysms occurred.

*Comment.* In this patient the resemblance of the pain to that of myocardial infarction was at first very striking. The exact mechanism of the pain was somewhat obscure but it seems likely that the proximal pouch became twisted in some way and precipitated the violent attacks of constrictive pain. The possibility that the coexistence of coronary disease may have influenced the distribution of the pain of gastric origin will be discussed later.

**Miscellaneous Disorders of the Stomach.** *Diverticulum.* I have observed only 1 patient in whom this disorder caused chest pain and this case had been reported elsewhere.<sup>11</sup> The pain was severe and the clinical picture was dramatic, resembling somewhat that of the patient just described who had a cascade deformity of the stomach. However, the patient with the diverticulum had had recurrent attacks for many years and an erroneous diagnosis of angina pectoris had been made.

Severe chest pain with radiation into the neck, shoulder or arm is quite exceptional in patients with gastric diverticula. However, mild substernal burning or pressure, *i. e.*, pain resembling that of angina pectoris in location and quality (but not in the precipitating factors) is not unusual. Discomfort of this type occurred in several of the cases reported by Bonham,<sup>5</sup> Reich<sup>18</sup> and Reineke.<sup>20</sup>

*Trauma to the Stomach.* CASE 1. A white male, 48 years of age, 15 years before had fallen on a sharp surveying pin which had penetrated the abdominal wall and stomach which were immediately repaired by operation. During the next year he had frequent seizures of pain in the left side of the neck induced by eating. These gradually became less frequent but he began to have attacks of a milder "pressing" pain in the left lower chest, anteriorly, in the precordial area. The discomfort was partially relieved by turning to the right side, by sitting, and especially by belching. Physical examination and electrocardiograms revealed no abnormalities. Fluoroscopic examination was negative except for aerophagia. Attempts were made to reassure the patient but he insisted that he had "heart trouble" and attempts to convince him otherwise were unavailing.

*Postoperative Obstruction.* CASE 2. A female, aged 42, had a subtotal gastric resection for peptic ulcer, gastro-enterostomy being performed. Ten days later she began to have severe cramping pains in the left lower chest, anteriorly, radiating to the left side of the neck and into the proximal part of the left arm. The pain was aggravated but not induced by deep breathing and was usually relieved by vomiting. At first the attacks were induced by ingesting liquids. A few days later she could take water comfortably but had pain upon eating small quantities of any solid food. Fluoroscopic examination displayed obstruction of the artificial opening between the stomach and the jejunum. Atropine decreased the frequency and the severity of the attacks. As time passed she gradually improved and about 6 weeks after the operation the pain disappeared entirely.

*Comment.* It is uncertain whether the pain in this patient was due to edema or to spasm of smooth muscle at the site of the gastro-enterostomy. The prompt beneficial effect of atropine suggests the latter mechanism.

*"Acute Indigestion."* CASE 3. A 28 year old white male had been drinking excessively for 48 hours and toward the end of the spree ate a large meal consisting chiefly of barbecued meat. Six hours later he was awakened with a violent squeezing pain, radiating into the neck and to both shoulders. The pain would last for a few seconds and then improve for perhaps a minute and then become more intense again. It was aggravated by breathing. He vomited 4 times during the next hour but this was followed by only temporary relief. He was then brought to the hospital where he was found to be in a state of collapse, the systolic and diastolic blood pressures being 85 and 70 mm. of mercury, respectively, while the heart rate was 45 beats per minute. In spite of his youth myocardial infarction was suspected and an electrocardiogram was made which revealed about 1.5 mm. elevation of the S-T segment in Lead 2, with a diphasic T<sub>2</sub>. After the pain had endured for 5 hours, improvement set in and within 16 hours after the onset of symptoms he felt completely well. However, the electrocardiographic changes persisted. When he was questioned carefully it was learned that a year before he had been in an automobile accident and had fractured several ribs in the region of the left axilla and precordium.

*Comment.* It seems clear that in this patient the acute episode of pain was the result of irritation of the stomach, resulting from alcohol and from the injudicious intake of food. The bradycardia, acute hypotension and clinical appearance of collapse were brought about by the vagal stimulation which often accompanies acute gastric disturbances. The misleading electrocardiographic changes were probably due to an old scar on the surface of the heart brought about by contusion at the time of the automobile accident, as described by Beck.<sup>2</sup>

*Discussion.* Practically all of these patients who had chest pain arising from disorders of the stomach believed that they were suffering from cardiac disease. In some instances this conclusion had been drawn by the patient himself while in other cases the diagnosis had been made by his physician. Although in some of the patients it was clear

from the outset that no disorder of the heart existed, in others, and particularly in those with the various deformities of the stomach, the differentiation from angina pectoris or from myocardial infarction was very difficult. Among the points which have been helpful in making such a distinction in this series of patients are the following:

The location of the pain is of relatively little differential value. However, when the point of greatest intensity is in the epigastrium, the left hypochondrium or behind the lower ribs, the stomach is a more likely source than the heart. The reverse is true when the area of greatest severity is in the neck, the precordium or the upper substernal region. Pain behind the lower sternum is a common result of either condition.

The duration of pain from the stomach is more variable than is the pain of angina pectoris, which rarely endures for less than 1 minute or for more than 1 hour.<sup>12</sup>

The quality of the pain is of relatively little value in differentiation because constrictive pain, feeling of pressure, and burning discomfort may occur in either condition. Apparently a dull aching sensation is more commonly of cardiac than of gastric origin.

Since both pain arising in the heart and that produced in the stomach may vary from a barely perceptible discomfort to intense agony, the factor of severity is of practically no diagnostic value. However, the constancy of the severity during a given attack is occasionally a helpful guide. Stomach pain may resemble labor pain in coming in "waves" of increased intensity, separated by short intervals of comparative comfort.

The precipitating factors of the pain are of great diagnostic value but may occasionally be misleading. Thus, while distress regularly produced by effort is a characteristic feature of angina pectoris, it is not found in every case. Under exceptional circumstances pain induced by exertion may occur in patients with disorders of the stomach. Jones<sup>15</sup> reported a patient with pain produced not only by eating but occurring regularly when walking a distance of 50 yards. Following resection of an hiatal hernia the patient was able to walk long distances without discomfort.

The tendency of pain to occur when the stomach is distended, and to be relieved by belching, is a characteristic feature in many patients with disorders of the stomach. However, similar events may occasionally occur in patients with angina pectoris and are probably related to the reflex vasoconstriction of the coronary arteries, which may result from stimuli arising in the stomach.<sup>9,10</sup> However, as a general rule, a pain which can be regularly reproduced by distending the stomach with air is likely to be of gastric origin.

Pain related to swallowing or to breathing is not unusual in patients with gastric disorders and may occasionally occur in subjects with recent myocardial infarction. However, these acts rarely, if ever, induce or aggravate attacks of angina pectoris.

Pain arising in the stomach is frequently influenced by posture and, depending on the nature of the disorder and the position of the

lesion, such pain may be affected either favorably or adversely by almost any position of the body. Typically, the discomfort due to herniation of the stomach through the esophageal hiatus tends to come on in the recumbent position. However, anginal attacks, when they occur at rest, are likewise more apt to appear during recumbency and may be relieved by the upright position.<sup>12</sup> This seems to be the only relationship of angina pain to posture. Hence, a pain which is aggravated by lying down—irrespective of the exact recumbent posture—may arise either from the stomach or from the heart, but a pain which is worse in the left lateral position than the right (or the reverse), or which is aggravated by sitting or standing, is more likely to arise in the stomach than in the heart.

Gastric pain is frequently precipitated by alcoholic liquors and often relieved by the atropine group of drugs which have little effect on cardiac pain. Nitroglycerin may benefit pain arising from the stomach but the effect is not likely to be as striking as in the case of anginal pain.

Obviously the electrocardiogram and the radiologic examination of the stomach may be of the greatest value. However, these methods of study frequently yield negative or inconclusive results and may need to be carried out during the attacks of pain in order to be of maximal diagnostic value. Furthermore, minor abnormalities due to healed or insignificant disorders may be erroneously interpreted. Hence, the common tendency to rely almost entirely on these methods and to make only a superficial inquiry into the clinical qualities of the pain is one of the most common causes of incorrect diagnosis and inadequate treatment.

The differentiation of pain arising in the stomach from that of esophageal origin is often impossible from the history alone. Pain of burning quality may arise from either organ\* but is more typically of esophageal origin. Localization of discomfort in the epigastrium or behind the lower ribs on the left is more common when the stomach is at fault, but either organ may give rise to substernal distress or, less commonly, to pain in the precordium, left shoulder, or arm. Although pain arising in the stomach is more likely to be affected by posture, esophageal discomfort is often induced more readily by swallowing when the patient is recumbent than by the same act when the subject is upright. The most valuable differential points are the greater likelihood of dysphagia or of pain on swallowing in patients with esophageal lesions and the tendency for belching to relieve pains arising from the stomach. When esophageal pain is related to the ingestion of food it is likely to occur *during* eating while gastric pain more commonly sets in *after* eating. These several points may be of some value in providing a clue as to the most likely site of the pain, but in the majority of instances radiologic or other special studies are necessary before an accurate decision can be made as to whether the esophagus or the stomach is at fault.

\* The recent studies of Wolf *et al.*<sup>27</sup> indicate that burning pain probably does not arise from the gastric mucosa *per se* but that disorders of the stomach may lead to it indirectly by causing regurgitation of the gastric contents into the esophagus.

Attempts to differentiate from each other the several different disorders of the stomach which may cause pain in the chest are likewise fraught with considerable difficulty. . Apparently ulcer and carcinoma of the stomach do not usually need to be considered. Despite their relative frequency neither of the conditions was responsible for pain referred to the chest in any instance in the present series. Most of the cases fell into 1 of 2 groups: (1) functional distention of the stomach due to pylorospasm, aerophagia, ptosis or a combination of these factors, and characterized by mild pain, relief by belching, a tendency for the pain to be aggravated by lying on the left side, the coëxistence of palpitation, pronounced relationship to emotion, the presence of anxiety reactions out of proportion to the intensity of the pain, and the frequent occurrence in young to middle-aged females; or (2) disorders dependent on abnormal pouches in the fundic end of the stomach, including herniæ, diverticula and cascade deformities, and characterized by pain of mild to intense severity, radiating to the left side of the chest, shoulder and arm, spasmodic and intermittent character, aggravation by ingestion of alcoholic beverages, marked relationship of the pain to eating and to the position of the body (the posture of maximum severity varying in different subjects), and a tendency to simulate closely the pain of angina pectoris or of myocardial infarction. The differentiation between the several disorders of the latter group can usually be made only by careful and repeated radiologic examination with observation of the stomach in various positions.

The frequency of the coëxistence in a given patient of pain due to coronary disease, and of pain due to gastric disorders, has been stressed in a previous communication<sup>12</sup> and is well illustrated by the patient with the cascade stomach cited in the present report. It seems probable that in such instances the tendency of the two different pains to be referred to the same general regions is related to the factor of summation as suggested by Jones,<sup>15</sup> and by Boas and Levy.<sup>4</sup> According to this concept the existence of subthreshold afferent stimuli from one region tends to sensitize the corresponding segment of the spinal cord to stimuli reaching it from adjacent segments. Such an hypothesis accounts for the observation by Jones,<sup>15</sup> who found that in a patient with a left cervical rib inflation of a balloon in the esophagus caused pain not only in the substernal area but discomfort in the left shoulder and arm. Deep pressure just above the left clavicle, in the region of the cervical rib, reproduced the pain. Following removal of the cervical rib inflation of the balloon in the esophagus caused discomfort only in the substernal region. Jones likewise pointed out that in the presence of operative abdominal scars pain produced by distention of the esophagus or stomach was frequently referred to the site of the scar. The hypothesis of summation of stimuli accounts for such observations, as well as for the tendency for patients with both coronary disease and gastric disorders to have pain produced by either disorder referred to the same general areas. From a practical point of view it would therefore seem advisable to seek with especial care for coëxisting angina pectoris when a patient has pain of gastric

origin referred to the left arm, and conversely to suspect coëxisting abdominal disease when the pain of angina pectoris radiates to the abdomen.

**Summary.** The clinical findings—with special reference to the qualities of the pain—have been analyzed in 24 patients with pain in the chest due to disorders of the stomach. In a number of subjects the pain radiated from the precordial or substernal region to the left shoulder and arm, and also resembled in character and in intensity the distress caused by disease of the coronary arteries. Various distinguishing features between pain of gastric origin and that arising from the heart have been discussed. The diagnostic value of radiologic examination during the attacks of pain and of reproducing the symptoms by distending the stomach with air have been emphasized. The necessity for a meticulous analysis of the patient's story of the pain, with especial attention to the various precipitating, aggravating and alleviating factors has been especially stressed.

Among the cases reported in the study are the following:

1. An individual with perforation of an hiatal hernia.
2. A man with mild angina pectoris who subsequently developed violent pain in the chest and left arm, due to cascade deformity of the stomach.
3. A woman with severe postoperative chest pain due to intermittent obstruction of the gastro-jejunal communication.
4. A patient with genuine "acute indigestion" (due to dietary indiscretion) simulating myocardial infarction.

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## PENICILLIN IN THE TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA

### A PRELIMINARY REPORT

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THIS preliminary report on the treatment of intractable bronchial asthma with penicillin records our observations of 2 patients whose treatment was completed 5 months ago and 4 months ago respectively.

**Case Reports.** CASE 1. Le., a woman 45 years of age, with a strongly allergic family history, who has been severely asthmatic since early childhood. For the past 15 years her asthma had been so severe that she required at least 1 injection of epinephrine every night and on very many occasions many injections both day and night. Tests for allergic sensitivity by the intracutaneous method revealed strongly positive reactions to 42 allergens including several inhalants and many foods. Rigid environmental control including several weeks sojourn in a relatively dust-free, air-conditioned room, together with rigid avoidance of all positive reacting foods, occasioned no improvement in this patient's asthma.

For many years she showed clinical and Roentgen evidences of disease of the maxillary sinuses; but it was extremely difficult to decide whether this was a concomitant part of the allergic picture or primary. During all of these years repeated and almost daily examinations of the chest revealed a profusion of asthmatic râles. The asthmatic state was ever present, but despite this the patient never developed status asthmaticus, and had not become emphysematous. There never had been clinical manifestations of cardiac disease.

She has had at least 4 episodes of pulmonary infection, undoubtedly initiated by bronchial plugging, followed rapidly by atelectasis and pneumonic consolidation. On other occasions the sudden onset of localized pleural pain and fever had prompted the immediate administration of epinephrine which probably had a favorable effect on relieving bronchial obstruction, thus preventing the development of pneumonic consolidation.

In June 1942, this patient came under the care of one of us (R. A. C.) at the Roosevelt Hospital. She was placed in an air-conditioned room and given by intent certain of the essential foods to which she was demonstrably allergic by tests. There was neither relief of asthma nor an exacerbation of symptoms during this time. While in the hospital she was tested by passive transfer (Prausnitz-Küstner technique) to 42 of the substances to which she had reacted by direct intracutaneous test. All of the food allergens failed to give any reaction.

Following discharge from the hospital she remained on an unrestricted diet with neither relief nor aggravation of symptoms. At this time she was given an autogenous vaccine made from the organisms obtained by antral irrigation, but with no effect.

In November 1942, she was readmitted to the Roosevelt Hospital for a bilateral Caldwell-Luc operation which was performed by Dr. R. C. Grove. Following this, the patient experienced the usual transitory improvement for several weeks. Since operation she has been free of upper respiratory symp-

toms. Culture of the antral tissue removed at operation showed *Staph. albus* predominating and *Strep. viridans*.

Early in June 1944, the asthma continuing unabated, the patient was admitted to the Hospital of the University of Pennsylvania, and it was decided to treat her with penicillin, with Dr. Harrison Flippin collaborating. Naturally, we were fearful of giving penicillin, particularly by the intravenous route to this highly allergic patient, and all the more so because she was very sensitive to house dust. Many such patients are allergic to fungi and molds. We did not wish to combine a local anesthetic with the drug given intramuscularly, because we had some evidence that this patient in the past had been allergic to cocaine and its derivatives. We tested her for allergic sensitivity to penicillin in saline suspension, and after we obtained no reaction, we started treatment with this material. Prior to this, sputum culture showed a non-hemolytic streptococcus, which *in vitro* was found to be moderately penicillin sensitive, and this encouraged us to proceed.

She was given intramuscular injections of penicillin every 3 hours, 100,000 units every 24 hours, until she had received a total of 1,375,000 units. At this point the patient developed a violent urticarial reaction with fever, adenopathy, and swelling of the joints. This reaction which had all of the essential characteristics of serum disease persisted for 6 days. Following this she was relieved of asthma for more than 3 months to the extent that she did not require epinephrine. However, although the patient had no subjective symptoms, frequently repeated examinations of the chest showed almost always the presence of a few sibilant râles. Serum for passive transfer was obtained about 1 month after the urticarial reaction and was negative to the penicillin used in the test. This was not identical with the lot used in treatment.

Early in October 1944, an acute upper respiratory infection occurred, with prompt recurrence of bronchial asthma again requiring frequent administrations of epinephrine. This recurrence was complicated once more by severe localized pleural pain and fever. The immediate use of sulfadiazine in full doses, and frequent administration of epinephrine was followed by relief of pleural pain, with disappearance of frictions over this area, and subsidence of fever in 48 hours. Following this administration of sulfadiazine, she had a mild urticarial reaction, similar to that which she had had on numerous occasions following sulfonamide therapy. Since this time the patient has been free of asthma subjectively, but a few sibilant râles can usually be heard whenever the lungs are examined.

CASE 2. Wi., a young woman 26 years of age with a definite family background of allergy. Asthma began at the age of 10 years and occurred in periodic attacks at any and all times of the year and only following respiratory infections. Over the years the attacks have become more frequent and more prolonged. When first seen in June 1943, dyspnea, cough and wheeze had been continuous for 4 months. The intracutaneous skin tests were completely negative to all the usual inhalant and food allergens and clinical observation could not confirm any ingested food as a factor. Chest examinations showed typical sibilant râles throughout with a moderate grade of emphysema and with a reduction of vital capacity of 25% after epinephrine injection. The heart was normal. Sputum cultures showed pneumococcus as the predominating organism. Clinical and Roentgen examination of the sinuses disclosed bilateral antral involvement especially marked on the right. Under symptomatic treatment and vaccine therapy there was no improvement, and in June 1944 she reported that her dyspnea had been continuous throughout the previous winter with one "cold" after another. Coughing was severe, especially at night, and sleep was consequently greatly disturbed. Examination at this time confirmed the previous findings of antral occlusion. Right antral irrigation yielded mucopus with occasional eosinophils. *Strep. viridans* was recovered from the culture. Penicillin therapy was employed at the rate of 100,000 units daily (12,500 every 3 hours) for 10 days, ending July 8, 1944. Some improvement was observed during hospitalization. Two

weeks later she reported no asthma and examination of the chest disclosed no adventitious sounds even on forced respiration. Three months later (October 1944) examination showed occasional sibilant sounds after forced expiration but there was no subjective or objective dyspnea and the vital capacity was within normal limits for her height and weight. To date (Nov. 9, 1944) she has had no return of asthma.

This patient had less severe and less prolonged asthma than Case 1, but it had become persistent and intractable for over 6 months. However, both patients belong in the same category in that infection appeared to be the important etiologic factor.

It is obvious that penicillin should be of no value whatever in the treatment of asthma due to air-borne or ingested substances. It is equally apparent that penicillin can be expected to have no therapeutic effect in those patients who have both extrinsic and intrinsic bronchial asthma, if the extrinsic factors are not controlled.

Many young children of allergic soil who develop bronchial asthma early in life have uncomplicated extrinsic asthma. As they grow through adolescence into adult life, and continue to have asthma, the perpetuation of their disease may be the result of acquired bacterial infection. Many of them, then, have both extrinsic and intrinsic allergic disease. Some exhibit strongly positive reactions to many allergens, as the result of childhood sensitivities, but if these cannot be confirmed by passive transfer they may be of doubtful etiologic significance especially when clinical trial fails to produce any symptomatic response. It is reasonable to believe that this is illustrated by Case I of this report.

Those individuals who develop bronchial asthma in adult life, and particularly those who become asthmatic in the 4th decade of life or later, are usually examples of intrinsic asthma, regardless of whether or not the family history is positive for allergic disease. It is possible that penicillin may be found to be of therapeutic value in this group, particularly if the organisms recovered from the bronchial secretion, or from the upper respiratory tract are sensitive *in vitro* to penicillin.

In the presence of clinically demonstrable infection in the paranasal sinuses, or in the presence of other infective foci having an etiologic relationship to bronchial asthma, it is altogether probable that surgical drainage or eradication of such foci may be necessary in addition to the use of penicillin or of any other therapeutic agent to assure any appreciable duration of remedial effect. This remains for the future to decide. However, since penicillin therapy has been shown to have a favorable effect in certain types of purulent sinusitis it may ultimately be shown to be effective in the control of hyperplastic sinusitis of allergic individuals.

We are well aware of the difficulties of evaluating the therapeutic effect of any procedure in the treatment of bronchial asthma. This disease is characterized by spontaneous remissions. Many patients with continuous asthma are improved by hospitalization even if nothing else is done for them. Many asthmatics have periods of remission of considerable duration after acquiring an intercurrent, febrile infec-

tion. In 1813, Dr. Nathaniel Chapman,<sup>1</sup> then Professor of Physic of the University of Pennsylvania, told his students that for some years it had been his custom to send his patients with intractable asthma to the Mediterranean Littoral, there to contract malaria and hence be relieved of asthma. The induction of artificial fever in the hands of Miller and Piness,<sup>4</sup> Feinberg and his co-workers,<sup>2</sup> and one of us (S. S. L.) in collaboration with Stewart,<sup>3</sup> produced no such fortuitous result.

While it is possible that the severe urticarial reaction which our Case 1 had was responsible for her remission, it is only fair to say that this patient had had several similar but less severe reactions from sulfonamide therapy without any remission at all.

**Comment and Conclusions.** Of the 2 patients with intractable continuous bronchial asthma, in Case 1, following treatment, there was complete remission of asthmatic symptoms for almost 4 months, although very frequent examinations of the lungs during this time revealed the almost constant presence of sibilant râles. No such remission had occurred in the 15 previous years. An acute upper respiratory infection produced the expected recurrence of asthma; its subsidence has been followed by subjective relief, although sibilant râles are usually present. In Case 2, 4 months have elapsed with no subjective asthma.

Twenty-five additional patients with intractable asthma have either been treated with penicillin very recently or are under treatment by us at the present time. It is impossible at this time to know what results, if any, will be achieved in this group. But already it has become evident to us that penicillin is not a panacea for all cases of asthma due to infection, for some patients have shown no improvement after penicillin therapy.

There is no reason to believe that penicillin will be of the slightest benefit in extrinsic bronchial asthma. It is possible that this drug may be found to be helpful in treatment of two groups of asthmatics: those with both extrinsic and intrinsic asthma provided the extrinsic factors are properly controlled, and those who only have intrinsic disease.

It is possible that penicillin may be of value in that group of cases in which the bacteria recovered from the sputum or from the upper respiratory tract are shown to be sensitive to penicillin *in vitro*.

It will require the careful and detailed study of many patients by many groups of observers over a considerable period of time to determine whether or not penicillin will yield results of sufficient permanency as to warrant its use in the treatment of intrinsic bronchial asthma.

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# PROGRESS OF MEDICAL SCIENCE

## PEDIATRICS

UNDER THE CHARGE OF  
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### THE INTRA-DUODENAL SECRETIONS IN CHILDHOOD

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AN aspirating tube passed into the duodenum when the stomach is empty, during the so-called "interdigestive" period, will usually secure on suction a few cubic centimeters of clear golden secretion having a tendency to foam. Analysis of such fluid by the laboratory gives most helpful information to the pediatrician puzzled by digestive disorders otherwise obscure. This Review is designed to summarize the present state of knowledge concerning the intra-duodenal secretions during infancy and childhood. The current wave of intubation reports has furnished much of the clinical data, but the background of general principles derives of necessity from experiments on animals and adults.

*Intubation* of the child's duodenum is not difficult, once the technique has been mastered. Good descriptions of the technique have been furnished by Müller,<sup>58</sup> Andersen,<sup>6</sup> and Shwachman, Farber and Maddock.<sup>74</sup> Fluoroscopic control facilitates the procedure. Early workers in the field (Hess,<sup>44</sup> Freudenberg<sup>33</sup>), as well as others more contemporary,<sup>6,66,74</sup> have seemed to prefer a slim single-lumen Nos. 10 or 12 French tube of flexible rubber, though Chenoweth<sup>18a</sup> chose one equally narrow but with 2 lumens (Miller-Abbott<sup>57</sup> type). For intubation of the duodenum itself either variety is satisfactory. The jejunum and ileum can be more readily reached with a double-lumen tube having an inflatable bag at its tip.

The nature of the manipulation utilized to withdraw the duodenal contents makes it well-nigh impossible to be sure that the volumes withdrawn represent the total amount secreted during the observation period. Saliva and gastric contents tend to leak into the duodenum; to forestall this it has been recommended that the contents of the stomach be aspirated independently and simultaneously through a second tube reaching into the stomach.<sup>1</sup> Another suggestion has been to introduce a Miller-Abbott double-lumen tube into the duodenum, with a balloon inflated distal to the ampulla of Vater, in order to block leakage of any of the duodenal contents into the jejunum. This latter procedure sometimes causes unpleasant local pains, and on occasion has caused a constitutional shock-like reaction, most alarming to the bystander.<sup>18b</sup> For that reason, among others, it is wise to have the actual intubation of the child's duodenum

performed by a physician, who should remain close by the subject until the entire procedure has been completed.

**The Duodenal Fluid.** Any critical survey of the digestive phenomena which take place in the duodenum should consider that the food materials reaching it have already passed through the mouth, esophagus and stomach, and that they have been masticated and squeezed, exposed to salivary and gastric enzymes, mixed with mucus and hydrochloric acid, and otherwise made ready for digestion by the small bowel. Some of the threads in the complex pattern of physiologic interrelationships linking duodenum and stomach have been untangled and laid clear for inspection;<sup>5,9</sup> others remain to be traced. One should also remember that the chymous food released by the stomach flows through the duodenum with great rapidity. Only on chance occasions do Roentgen rays after a barium feeding succeed in visualizing the full contour of the duodenum. The secretions may blend with the food while passing through, but the chemical interactions take place further down.

The duodenal juice may be viewed as a pool or composite of secretions forming simultaneously (1) from Brunner's glands and the duodenal mucous membrane (*succus entericus*); (2) from the pancreas (*amylase, lipase, trypsin*); and (3) from the liver, gall bladder and bile ducts (*bile, mucus*). The relative percentage of components derived from each of these separate sources at any one time depends upon a variety of fluctuating mechanisms, constitutional as well as local. Nervous and hormonal control operate jointly as control mechanisms.<sup>9,96</sup> In addition, the duodenal mucous membrane along with that of the jejunum seems to elaborate several hormonal principles—*secretin, pancreozymin, enterogastrome, enterocrinin, cholecystokin* and *villikin*—which play a part in regulating the functioning of other portions of the gastro-intestinal tract. Berger's<sup>12</sup> continuous studies with intubated adults have shown that the fasting duodenal secretion wells out at irregular rhythmic intervals 5 to 50 minutes apart. Pediatric experience is that successive applications of suction at 5 to 15 minute intervals usually secures interdigestive fluid in inconstant amounts before resistance is encountered to the further drawing out of the plunger of the syringe. Specimens contaminated with gastric juice will be paler, more acid, floccule-containing, and of greater volume than those free from such admixture. The reader who desires detailed information concerning recent work with the duodenal enzymes of children in health and disease should refer directly to the contributions of Klumpp and Neale,<sup>50</sup> Andersen,<sup>6</sup> Kajdi and Davison,<sup>48</sup> Farber, Shwachman and Maddock,<sup>26,53,74</sup> and Philipsborn, Lawrence, Gibson and Greengard.<sup>65</sup> He should remember, however, that a number of earlier workers have made pioneer contributions in the same field, notably Hess,<sup>44</sup> Schiff, Eliasberg and Mosse,<sup>73</sup> Davison,<sup>22</sup> Müller,<sup>58</sup> and Freudenberg.<sup>33</sup>

The difficulty in collection is only one of the reasons why examination of the duodenal contents must be but semiquantitative. Each of the component elements which go to make up the interdigestive duodenal fluid seem to spontaneously fluctuate both in potency and rate of secretion. Wide variations in color and in relative proportions of bile acids to pancreatic enzymes are exhibited by the same individuals from hour to hour, suggesting, as has been demonstrated more explicitly with adults, that the rate of formation of duodenal fluid during fasting proceeds erratically and irregularly. Older children tend to produce more potent secretions at faster rates than do infants, and individual differences have been commonly noted.

*Rate of Formation.* The rate of appearance of duodenal fluid during fasting, as judged by the flow from the tube, varied from 4 to 31 cc. per hour (mean 8 cc.) in Kajdi and Davison's<sup>48</sup> 10 normal infants. The 7 normal infants and young children of Philipsborn *et al.*<sup>65</sup> produced from 8 to 25 cc. per  $\frac{1}{2}$  hour in the resting state. Farber *et al.*<sup>26</sup> noted that in infants under 2 months the flow varied from 1 to 5 cc. per hour and was usually near 3 cc.; in infants of 1 year this rate was doubled, and in older children often increased eightfold. The amounts were not affected appreciably by crying or excitement. There was no decrease in *chronic nutritional disturbance*, and a questionable increase in patients with *celiac disease*.

*Pancreatic fibrosis* seems to be the one condition existent in the pediatric age period in which the fasting duodenal contents are persistently small in volume and strikingly different from the watery contents obtained from all other individuals studied. As Farber<sup>26</sup> describes it, the material is thick and sticky; it adheres to the glass rod or to the side of the test tube and falls very slowly. This gross appearance has a counterpart in the histologic appearance of inspissated material in the acini and ducts of the pancreas.

*Stimulation of pancreatic flow*, as affected by *humoral* or *neural* mechanisms, becomes reflected in an increase in duodenal fluid. Both in animals and man stimulation with secretin produces a large volume of pancreatic juice rich in bicarbonate but poor in enzymes, whereas parasympathetic (vagal) stimulation evokes a scant flow of thicker juice poor in bicarbonate but rich in enzymes. Comfort and Osterberg<sup>20</sup> have demonstrated both of these effects very clearly for adults, using mecholyl chloride (acetyl-beta-methylcholine chloride) as the vagal stimulant.

The effect of *secretin* upon the duodenal fluids of children has been studied by Maddock *et al.*<sup>53</sup> and by Philipsborn *et al.*,<sup>65</sup> who found that secretin may be injected repeatedly into the circulation of infants and children without ill-effects. Maddock noted a secretory augmentation within 3 to 5 minutes, which in normal individuals reached a peak of about double the rate inside of 20 minutes. Six patients with chronic nutritional disturbance and 2 patients with idiopathic celiac disease showed an excellent response to secretin, but the flow was not increased in 7 children with pancreatic fibrosis. Philipsborn's 7 normal subjects also had a doubling of the rate of flow  $\frac{1}{2}$  hour after stimulation with intravenous secretin or with intra-duodenally introduced N/10 hydrochloric acid. Results with *mecholyl chloride* in children have not been published.

*Specific Gravity.* The specific gravity of 10 specimens of fasting duodenal contents collected from 9 infants ranged from 1.002 to 1.010 and had a mean of 1.006 (Kajdi and Davison<sup>48</sup>). These results are essentially identical with the range 1.002 to 1.008 reported for normal adults by Rehfuess and Williams.<sup>63</sup>

*Buffer Strength.* Freudenberg<sup>33</sup> showed that the buffer substances in the infant's duodenal fluid consist largely of bile acids and their salts, with the glycocholates being more abundant than the taurocholates. In the duodenal juice from a 3 months old infant the total concentration of bile acids was about 0.18 gm. per 100 cc.; while the juice from a 2 year old child contained about 5.5 gm. per 100 cc. He observed that in the pH zone 4.5 to 6.5, 10 cc. of duodenal juice will neutralize 1 to 2 cc. of N/10 hydrochloric acid. From this datum and the known buffer power of cow's milk he then computed that elevating the pH of 100 cc. cow's milk from 4.5 to 6.5 would require some 380 cc. of duodenal juice. Since

cow's milk<sup>23</sup> evokes a more abundant acid secretion on the part of the stomach than does breast milk, the formula-fed infant must elaborate a much more liberal supply of alkaline small intestinal juice than does the breast-fed baby, in order to counteract the greater acidity and greater buffer of cow's milk. Freudenberg attributed the lower duodenal pH values found in intestinal upsets to temporary impairment of the neutralizing duodenal secretions during the acute illness.

*pH.* From a review of the early literature Freudenberg<sup>23</sup> concluded that the intra-duodenal hydrogen-ion concentration of the *healthy* infant and child when fasting usually falls slightly on the acid side of neutrality, between pH 6 and 7, and that decidedly alkaline reactions are not encountered, even though the enzymatic activities of both crude pancreatin and refined trypsin are at an optimum at pH 8 and 9. Schiff *et al.*,<sup>73</sup> who kept one tube in the stomach to drain away the gastric contents while the tip of another tube was inside the duodenum, found the mean pH in 9 healthy infants during the fasting state (4 to 9 hours after a meal) to lie between 6.8 and 7.6. In 5 healthy infants, using similar precautions against gastric juice admixing, Kajdi and Davison<sup>48</sup> found a mean of 7.8 (extremes 6.8 to 8.2). But in 2 hours after a meal the mean duodenal pH of these latter infants was lower, 5.6 (extremes 5.2 to 7). In over 80 children from 1 month to 12 years of age Klumpp and Neale<sup>50</sup> found that the pH at all ages had a striking tendency to remain fixed in the pH zone 6.5 to 7 in the fasting state, while after a cream meal (pH 6.8) the pH fell in a constant manner to an average slightly above pH 5. Maddock *et al.*<sup>53</sup> found the pH of the duodenal contents of infants and children before stimulation to vary from 6.8 to 8. After stimulation of the pancreas with secretin the pH was increased by approximately 0.5 in all subjects studied except in the patients with pancreatic fibrosis. The rise occurred in 10 to 20 minutes after the injection and persisted in many instances for as long as 40 minutes thereafter.

In the *acute gastro-enteritides* of infancy more acidic conditions prevail. pH values below 4 were noted by Schiff *et al.*<sup>73</sup> and by Müller.<sup>58</sup> Davison<sup>22a</sup> took duodenal readings at postmortem on 11 infants who had succumbed to diarrhea and dysentery, and found the pH to range between 4.5 and 6.2.

A transitory *post-prandial* dip in the curve of intra-duodenal pH was observed in infants by both Schiff *et al.*<sup>73</sup> and by Müller,<sup>58</sup> during experiments in which milk was introduced directly into the stomach by one tube, and then duodenal fluid removed for examination through another indwelling tube at periodic intervals thereafter. The fall in pH was noticeable within 10 minutes, attained its maximum usually in 1 hour, and then slowly rose back to normal in 2 to 3 hours. With breast milk and most cow milk feeding mixtures the low point on the curve was usually at pH 4.5 to 5.5, always lower than the original pH of the milk when first given. With acidified milks, such as buttermilk, the low point was more often between pH 3.5 and 5.

Evidently the duodenal secretion when "pure" is neutral or slightly alkaline, but when "contaminated" with gastric contents is acidic. The exact pH status seems of minor clinical importance, even though the pancreatic enzymes have their optima for activity at neutrality or on the alkaline side, since these enzymes have but scant time within the lumen of the duodenum to be active. Food and secretions together stream quickly into the jejunum, where the succus entericus there elaborated mixes with and takes control over the pH of the material which comes in from the duodenum.



**Secretions Originating in the Duodenal Wall.** The large *Brunner's glands* lie in the duodenal mucosa and submucosa close to the pylorus. With human beings it has not been feasible to dissociate the secretions formed in this first part of the duodenum from those coming from the more distal part, which contains the ampulla of Vater and receives the external secretions of pancreas and liver. With experimental animals, however, it is not difficult to prepare surgical fistulæ which will discharge secretions derived solely from the first part of the duodenum and free from admixture with pancreatic fluid and bile. These fistulæ yield typical mucoid juice at a constant rate (Florey and Harding<sup>29</sup> obtained a steady 1.5 ml. per hour from a dog after food) in the absence of any mechanical or chemical irritation. In this regard this segment of the duodenum differs from other parts of the small intestine, in which, except for small amounts of "periodic" juice, fluid will be produced only after local stimulation. According to Florey, Wright and Jennings,<sup>30</sup> who surveyed the reported experiences in animals, this secretion is colorless or faintly yellow and clear, with specific gravity of about 1.008. Centrifuging occasionally gives an inappreciable deposit made up of cell débris and grayish mucin, derived probably from the goblet cells of the villi. The pH of specimens from most animals lies between 8.2 and 8.9 when collected in contact with air, with buffering power dependent mainly on bicarbonate. The content of total solids varies from 1.2 to 1.5%, with slightly more than half of the solids being inorganic in nature. This part of the duodenum reacts to secretin, and has a sensitive acetylcholine mechanism. Pilocarpine stimulates the flow of juice. The alkaline buffer capacity and the high mucin content of duodenal juice serve to protect the delicate villi of the first part of the intestine from damage by the acid stomach contents. It is not possible to say precisely what are the contributions of the Brunner's glands on the one hand, and of the villi and crypts of Lieberkühn on the other, though Brunner's glands may reasonably be held responsible for much of the duodenal secretions, especially the mucin.

Activation of the proteolytic factor in fresh pancreatic extracts by the juice of the small intestine is commonly explained in terms of a *kinase* or *enterokinase* contained in these juices. According to Wright, Jennings, Florey and Lium,<sup>36</sup> animal experiments demonstrate the presence of only 2 secretory enzymes in the *succus entericus* of the duodenum, namely enterokinase and amylase. According to these investigators the other enzymes there present (proteinase, peptidase, invertase and lipase) are endocellular in origin and originate in desquamated intestinal epithelium, or else have been poured in from the pancreas and other structures higher up in the gastro-intestinal tract. The mucosal amylase is probably weak compared with pancreatic amylase, though no exact figures are available, and therefore not of much significance. The enterokinase, on the other hand, appears to be powerful, and no doubt is of importance in activating the pancreatic juice as it emerges into the intestine. Whether duodenal juice contains more enterokinase than does juice from the rest of the small intestine, as Pavlov<sup>64</sup> believed, has not yet been determined. Wright *et al.*,<sup>36</sup> in a limited number of experiments, failed to find any differences between the digestive properties of secretion from the duodenal wall as compared with secretion from lower levels of the small intestine.

Kunitz and Northrop<sup>51</sup> are the most recent workers to study enterokinase. With crystalline trypsinogen the transformation of trypsinogen into trypsin proceeds as a spontaneous autocatalytic process, catalyzed by but independent of the concentration of enterokinase. With crude pan-

creatic extracts the activation by enterokinase is much more complicated, since these extracts contain a substance which inhibits trypsin, trypsinogen and chymo-trypsinogen. "Addition of kinase transforms the trypsinogen to trypsin which is partly inactivated by the inhibitor, thus decreasing the rate of the autocatalytic reaction. The free trypsin catalyzes the conversion of trypsinogen to form more trypsin and also catalyzes the conversion of chymo-trypsinogen to chymo-trypsin. If the method of activity determinations used determines both trypsin and chymo-trypsin, as is usually the case, the curves obtained when the activity of the solution is plotted against time are S-shaped but asymmetrical."<sup>81b</sup> Whether enterokinase exerts an activating influence on pancreatic lipase is not yet agreed upon.<sup>9</sup>

Enterokinase itself needs an activator *pro-kinase*, according to Waldschmidt-Leitz and Waldschmidt-Graser.<sup>90</sup> They noted that extirpation of the pancreas is followed by a great diminution in enterokinase activity of the small intestine. Babkin<sup>9</sup> criticizes their experiment as inconclusive.

**Exocrine Secretions of the Pancreas.** The chief enzymes contained in pancreatic juice are amylase, trypsin and lipase. There are no studies of recent vintage to confirm or contradict the traditional belief that the child's pancreas and duodenum give rise also to lesser enzymes such as lactase, sucrase, maltase and rennin in more than trace amounts. Any stimulus which provokes the appearance of any one of the three major enzymes simultaneously calls forth its two companions, both in animals<sup>39,41</sup> and in man.<sup>4,93</sup> Yet, interestingly, the type of foodstuff predominant in the diet bears some influence upon the relative proportions of these three enzymes. With young rats Grossman, Greengard and Ivy<sup>41</sup> found that a high carbohydrate diet produced pronounced increase in amylase content of the pancreatic secretion with decrease in trypsin, whereas a high protein diet evoked an elevation in trypsin. A high fat intake depressed the amylase without calling out more lipase. A low protein, high fat diet repressed all pancreatic enzymes, but when 1% choline was added to this diet the activity of all enzymes increased again. Michelson<sup>56</sup> has reported for human adults that the enzyme content of the duodenal drainage seemed to adjust itself similarly, within a few days, to similar dietary alterations. However, one unusual child having absent trypsin but normal lipase and amylase has been encountered by Farber, Maddock and Shwachman.<sup>26</sup> Trypsin failed to appear after two attempted stimulations with secretion. This boy, age not stated, "whose clinical picture was one of chronic nutritional disturbance," was the only instance of selective dissociation of this enzymatic triad encountered in some 140 infants and children, well and unwell.

The percentage composition of human pancreatic juice, as given by Fearon<sup>26a</sup> is as follows: organic solutes (lipids and enzymes), 0.6%; sodium, 0.25%; chloride, 0.35%; potassium, calcium, phosphates, sulfates, etc., in trace amounts. Stimulation of pancreatic flow by various factors has already been discussed.

**Amylase.** Amylases are carbohydrases which attack starches and glycogen. The lack of precise information concerning the internal molecular configuration of these substrates obscures the elucidation of the exact processes whereby they disintegrate when digested by the various animal and plant amylases. Pancreatic extracts are capable of digesting raw starch from corn, wheat and potato, whereas salivary amylase must be placed with cooked starches before its enzymatic activity begins.<sup>15a</sup>

Davison<sup>22c</sup> has elaborated upon the factors which make difficult the

titration of duodenal contents for amylase and trypsin. There is no general agreement as to the best definition of a unit. The viscosimetric method gives differences up to 20% in parallel titrations. Results are contingent also upon the substrates, for no two batches of starch (or gelatin) are exactly alike. End-products of the reactions, chemical accelerators and paralyzers, light and radiation, and differences in equipment alter and distort the activity of the enzyme. Davison<sup>22c</sup> cited four technical pointers made by Dr. D. H. Andersen in personal communications: (1) The position of the collecting tube in the duodenum is important and should be controlled by fluoroscopy. Specimens obtained just beyond the bend in the second portion of the duodenum may be 4 times as active as those collected either near the pylorus or in the terminal duodenum. (2) The time between dilution of the enzymes and its assay is a factor in accuracy, especially for trypsin. Titrations of fresh dilutions and of those allowed to stand for 1 hour or more are usually noticeably different. (3) If the patient is dehydrated, a much longer time is required to obtain the necessary 6 to 8 cc. of duodenal contents, and the enzymic assays sometimes are low. Diarrhea and malnutrition are often associated with a marked reduction in trypsin and amylase. (4) Diet and time after the last meal also influence the findings; fasting contents are more accurate. Davison<sup>22b</sup> noted that admixture of gastric juices greatly increased the amylolytic power of duodenal contents, not merely by stimulating the pancreas, but by some sort of specific accelerating action; with some specimens gastric contents increased the amylase activity eightfold. Acceleration of enzymatic starch hydrolysis by bile has been reported also.<sup>78a</sup> Viscosimetric techniques were used by Davison,<sup>22</sup> Andersen,<sup>6</sup> and Shwachman *et al.*,<sup>74</sup> taking as 1 "unit" the amount of enzyme required to decrease the viscosity of an appropriate starch mixture by 20% in 1 hour. Klumpp and Neale,<sup>50</sup> and Philipsborn *et al.*<sup>65</sup> estimated amylolytic activity in terms of the number of milligrams of dextrose developed in a solution of soluble starch over a given period of time.

Amylase activity is *normally* very low in the neonate, and increases gradually with growth into childhood. Many authors have presented data which portray this *age factor*—those of Klumpp and Neale<sup>50</sup> gathered from 74 normal children may be taken as representative. In round numbers, their mean fasting values for infants 1 to 30 months of age was 0.5 mg. (dextrose); for 3 to 12 months, 0.8 mg.; for 1 to 4 years, 2.5 mg.; for 4 to 6 years, 3 mg.; for six to nine years, 4 mg.; for 9 to 12 years, 3.5 mg. The range in values from which these means were compiled were extremely broad, indicating great spontaneous normal variations. When test meals of cream were given these investigators noted a slight increase in mean amylolytic activity, but the standard deviations of the individual readings were so great that such differences between the observed means cannot be considered significant.

Philipsborn *et al.*,<sup>65</sup> critical of Klumpp and Neale's presentation because "unfortunately values for enzyme activity were expressed without regard for volume," recalculated and reexpressed those results in terms of activity per unit volume of duodenal juice. (Search through Klumpp and Neale's original report fails to find any statement as to whether or not volume was taken into consideration.) The data when "reexpressed" by Philipsborn give means of less than 2 gm. dextrose per 100 cc. duodenal juice for the 1st year of life; about 6 gm. for 1st to 4th year; about 10 gm. for 5th through 8th year; and about 8 gm. for 9th to 12th year. Philipsborn's own data on 7 normal cases are in accord with Klumpp and Neale's figures.

Andersen's<sup>6c</sup> data on 54 normal children of assorted ages bring out the age factor even more vividly. Her mean figures, expressed in viscosimetric units, are as follows: age 0 to 2 months, 4.3 u.; 2 to 6 months, 25.3 u.; 6 to 12 months, 113.9 u.; 1 to 2 years, 177.4 u.; 2 to 5 years, 243.9 u. The standard deviation for each mean value was great, obscuring the diagnostic interpretation of individual low readings. As Andersen says, it would seem that the infant is not prepared to digest much starch before the 3rd or 4th month. Farber *et al.*<sup>26</sup> checked on the enzymatic status of 3 premature infants; 2 had very small amounts of amylase, and the 3rd had none. Philipsborn advised that pancreatic amylase not be considered deficient unless less than 0.5 gm. of dextrose is liberated by 100 cc. of duodenal juice in the first year of life, and less than 2 gm. after 1 year of age. Until a greater body of knowledge has been built up concerning normal values and normal physiologic functionings, a wise procedure in presentation of duodenal enzyme data would be to express them in both (1) units per cc. and (2) units per hour, as was done by Farber *et al.*

Kajdi and Davison<sup>48</sup> presented a 5½ month old infant who had the low average of 184 amylase units per cc. of duodenal contents when ill with *acute diarrhea* and *otitis media*; 1 month later, when *convalescent* and nearly well, his average had risen to 619 units. Of Andersen's<sup>6c</sup> 7 infants aged 6 to 12 months having *diarrhea*, 6 had amylase levels below 50 units; in contrast, of 11 control normal infants of comparable age, all but 1 were above the 50 unit level. With *chronic diarrhea* in children above the age of 6 months Andersen found the concentrations of amylase reduced to one-half to one-third below the normal controls. Andersen noted that 3 infants who presented the clinical picture of *marasmus*, with loose, dry skin, persistent *diarrhea*, muscular atrophy, severe loss of weight and inanition, showed a marked depression of the level of amylase. All showed enzyme concentrations within the normal range after clinical improvement. Farber *et al.*<sup>26</sup> failed to find impairment of enzymatic activity in 46 patients, aged from a few weeks to 7 years, suffering from various kinds of *chronic nutritional disturbance*.

The concentration of amylase in the duodenal drainage of patients with true *celiac disease* (idiopathic steatorrhea) has always been found to be normal.<sup>6,26,65</sup> It has been Andersen's<sup>6</sup> keen observation that many children diagnosed as celiac disease are not truly ill with classical idiopathic steatorrhea. Instead, as careful study reveals,<sup>7a</sup> these patients have *intolerance to starch* in the diet, give a low level of amylase in the duodenal juice, show starch in the stools with no excess of stool fat, and go through a relatively mild but prolonged clinical course. Low-starch diets—not the low-fat ones required for celiac disease (*vide infra*)—alleviate the symptoms and make for more normal growth.

*Lipase.*—Pancreatic extracts and pancreatic secretions are highly potent for the hydrolysis of the glycerides of the higher fatty acids, but their effectiveness is weak or negligible with substrates of esters compounded of organic acids with alcohols or carbohydrates. Consequently the term *lipase*, and not *esterase*, can be applied appropriately to this pancreatic factor. Wilstätter and Waldschmidt-Leitz,<sup>91</sup> Woodhouse,<sup>95</sup> and Glick and King<sup>36</sup> have shown, interestingly, that lipase extracts of animal pancreas often have very little activity when first made, but on standing in liquid solution or when significant amounts of certain substances are present promptly become actively hydrolytic. Among the activating substances are bile salts, egg albumin, the higher alcohols, boiled lipase solutions, and very small amounts of human and animal serum. These results have

been interpreted as meaning that the lipase is initially formed in a precursor zymogen state, as *pro-lipase*. However, Rabinowitch and Wynne<sup>67</sup> challenge this interpretation, claiming that pancreatic lipase does not require specific co-enzyme activators, and that the observed "activations" are due mainly to the buffering capacities of the added substances, which operate to shift the pH of the reaction-mixture from pH 3, at which the washed enzyme or *pro-lipase* is prepared, closer to pH 7, which is the optimum pH for pancreatic lipase activity.

During digestion the fat triglycerides are first emulsified by the bile and then split by the lipase. The fatty acids so liberated promptly go into a water-soluble freely diffusible combination with bile salts and are absorbed by the intestinal mucosa in this complex form.<sup>85</sup> Best and Taylor<sup>15a</sup> point out that not all the digestive lipase comes from the pancreas. In the absence of the pancreas or after ligation of its ducts as much as 50% of ingested fat may undergo hydrolysis by the action of the intestinal juices alone.

Goldstein and Roe<sup>37</sup> have *classified* the various commonly used methods of assaying lipolytic activity as being: (1) titrative, using alkali to measure the amounts of fatty acid liberated upon hydrolysis of a given substrate;<sup>19,92</sup> (2) stalagometric, using the rate of fall of drops of a solution containing enzyme, substrate (such as tributyrin),<sup>71</sup> and buffer; (3) manometric, measuring<sup>70</sup> the volume of CO<sub>2</sub> liberated from NaHCO<sub>3</sub> by the butyric acid formed on hydrolysis of tributyrin; and (4) electrometric, measuring the change in pH of a buffered solution as the enzyme acts upon ethyl butyrate<sup>83</sup> to liberate free fatty acid. One might cite in addition the turbidometric method of Craver and Walker,<sup>21</sup> which measures by photo-electric colorimetry the changes in turbidity occurring when serial dilutions of tributyrin are exposed to the enzyme for a 2 hour period. For descriptions of tributyrin methods see Goldstein and Roe,<sup>37</sup> and Free and Myers.<sup>32</sup>

Most of the recent work on pancreatic lipase in children has been based upon the titrative approach. This uses a standardized alkali solution to measure the fatty acids liberated within a standard period of time (usually 1 hour) from a standardized oil emulsion.<sup>50,65</sup> Lipolytic activity of the duodenal contents may be stated simply as the number of cubic centimeters of alkali solution required to neutralize the free fatty acids which form, or more indirectly in terms of calculated Willstätter "units."<sup>76,26,92</sup>

It is very difficult to set up standards for normal values from the reported findings of the different investigators. Not only have each group of workers introduced original modifications and simplifications of technique, but in addition their results are presented in a fashion far from uniform. One simple illustration to bring this out is the comment by Shwachman *et al.*<sup>74</sup> concerning substrates. An emulsion of olive oil prepared in their laboratories gave uniformly lower values than did parallel determinations of the same specimens performed with the commercial olive oil preparation used by Comfort.<sup>20</sup> As Free and Myers<sup>32</sup> emphasized, results of enzymatic analyses are better expressed in terms of comparison with control results gathered in the same laboratory, rather than in absolute figures which convey information difficult to consider away from their contexts. This recommendation is complied with in the paragraphs immediately following.

The accumulation of findings may be summed up by stating that wide variations *normally* occur with infants and children of all ages, and that there are no gradations in lipase activity associated directly with age. The sole exception to this latter statement is the data of Klumpp and Neale<sup>50</sup>

who found negligible lipase content in infants in the 1st year of life. Two of the 3 premature infants of Farber *et al.*<sup>26</sup> exhibited normal lipase; in the third activity was somewhat reduced. No significant diminution was found by Andersen<sup>6c</sup> in patients with chronic diarrhea or by Farber *et al.*<sup>26</sup> in children with *chronic nutritional disturbance*. The 4 *undernourished* infants of Philipsborn *et al.*<sup>65</sup> had markedly decreased duodenal lipase. This was judged to be a transient pancreatic insufficiency since all subsequently attained satisfactory nutritional status and 1 of them when subjected to a second duodenal study approximately 9 months after the original test had regained normal activity. All authors<sup>6b, 11, 26, 28, 66, 76, 82, 94a</sup> have described very low or wholly absent lipase in *cystic fibrosis* of the pancreas. Andersen<sup>6c</sup> states that low lipase figures may occur at times in other disease conditions, such as atresia of the common bile duct; therefore the finding of an absent or very low lipase is not of itself pathognomonic of pancreatic fibrosis.

In true *celiac disease* the dried stools may contain 30 to 60 % of lipid matter (the normal beyond infancy rarely exceeds 20 %<sup>45</sup>). Analysis shows this fat to be in the split form of fatty acids and soaps. Hence the fundamental lesion would appear to be an impairment of the absorption of fat through the intestinal wall, and not defective breakdown of fat within the intestinal lumen. Confirmation of this interpretation is given by the many reports of the unimpaired secretion of duodenal lipase by these patients.<sup>6c, 10, 26, 62, 63, 65, 81, 82</sup> Indeed, the presence or absence of pancreatic enzymes is the chief clinical diagnostic point for differentiating between celiac disease and cystic fibrosis of the pancreas. In the former disorder the pancreatic enzymes are present; in the latter they are absent, or nearly so. The suggestion has been made<sup>24</sup> that the pancreas normally produces some factor necessary for fat absorption, in addition to lipase, and that in celiac disease the pancreatic secretion is defective in this substance, but no presumptive evidence for the existence of such a hypothetical factor has as yet been brought forward.

*Trypsin.* Generally speaking, proteases can be divided into 2 classes, proteinases and polypeptidases. It was once thought that the proteinases—among them pepsin, trypsin and chymotrypsin—fragment the large molecules, such as whole proteins, proteoses and the peptones, down to the peptide stage only, and that the peptidases hydrolyze polypeptides and peptides to an ultimate mixture of amino acids. But enzymologists now base their differentiation upon the limited ability of peptidases to break off single amino acids only from one end or the other of the peptide chain, in contrast with the greater power of proteinases to dissolve amino acid linkages anywhere within the proteinous molecules. More recent studies, as summarized by Bergmann and Fruton<sup>13b</sup> and Johnson and Berger,<sup>47</sup> are demonstrating that the breakdown of proteins and protein products by enzymes in aqueous solution consists of a most complex set of processes with innumerable subsidiary equilibrium reactions acting one upon another. Working independently and in combination, co-enzymes, co-substrates and acid and base ions act to influence the directions and rates of the multiple component reactions which go on simultaneously. With synthetic peptide substrates pepsin, trypsin and chymo-trypsin exhibit characteristic differences in the conditions and rates of hydrolysis.<sup>13a</sup> It has been elucidated, chiefly by animal studies, that most of the proteolytic behavior of pancreatic juice is due to proteinases; the peptidases originating in the pancreas seem weak and few in number.

Pancreatic juice, as freshly secreted, will exhibit no proteolytic activity

until after coming in contact with acid or with enterokinase of the small intestine. This means that the proteinases of the pancreas are secreted in a *precursor* or *zymogen* form, in the same way as the pepsin of the stomach first appears as pepsinogen.

A few of the proteolytic principles in the pancreas have been *isolated* in relatively pure states. Thus, from the pancreas glands of cattle, Northrop and Kunitz<sup>61</sup> have crystallized 2 proteinases and 1 carboxypeptidase. The more potent of these crystalline proteinases is termed trypsin, the other, chymo-trypsin; they seem to be the principal proteinases in pancreatic juice. Neither alone can digest proteins very far, though acting jointly they split most proteins, such as casein, gelatin, edestin, peptone and denatured hemoglobin, down to the polypeptide stage. The existence of a third proteinase, "*hetero-trypsin*," in pancreatic extracts has been hypothesized by Bergmann, Fruton and Pollock.<sup>14</sup> Chymo-trypsin, which has an entirely different crystal formation from trypsin, will hydrolyze casein more completely and at different linkages than does crystalline trypsin. Crystalline trypsinogen and crystalline chymo-trypsinogen are the respective inactive precursors of these two active principles. Chymo-trypsinogen becomes activated by trypsin but does not respond to enterokinase.<sup>80</sup> The conversion of trypsinogen to trypsin is initiated by the enterokinase of the small intestine, and this co-enzyme in its turn is thought to require activation by a prokinase also present in pancreatic juice.<sup>90</sup>

Kunitz and Northrop<sup>51,61</sup> find the transformation of crystalline trypsinogen into crystalline trypsin to be accelerated by the addition of trypsin or enterokinase or by concentrated solutions of magnesium sulfate or ammonium sulfate. When trypsin is added to trypsinogen the reaction follows quite closely that of a simple autocatalytic reaction. The rate of activation depends on the pH and is maximum at pH 7 to 8. The reaction is complicated by the fact that an inert protein is also formed from trypsinogen in the presence of trypsin. The optimum hydrogen-ion concentration for digestion of casein by crude trypsin, crystalline trypsin and crystalline chymo-trypsin was found to spread as a flat maximum from pH 8 to 9. Kunitz and Northrop<sup>51c</sup> studied also the long-known substance in pancreatic extracts which inhibits the action of trypsin. They succeeded in isolating rod-shaped crystals of this inhibitor and hexagonal many-faced crystals of an inhibitor-plus-trypsin compound.

The complex nature of the pancreatic peptidase has been studied in some detail by Abderhalden and Schwab,<sup>1</sup> and Abderhalden and von Ehrenwall,<sup>2</sup> and the presence of a *leucin peptidase*, a *tyrosin peptidase*, and several *acylases*, has been demonstrated. Waldschmidt-Leitz and Kofranyi<sup>88</sup> have described a pancreatic "*protaminase*" or *carboxypeptidase*, which splits arginine from the carboxyl end of the clupein molecule. A *prolinase* or *prolylpeptidase*,<sup>3</sup> a *carboxypeptidase*<sup>8</sup> and a *dehydropeptidase*<sup>15</sup> have also been reported. The *carboxypeptidase* has been crystallized by Anson<sup>8</sup> and by Northrop.<sup>61b</sup> It seems to be secreted in the form of an inert and as yet unpurified precursor, *pro-carboxypeptidase*, which becomes activated when in contact with enterokinase or with trypsin. Descriptions of the pancreatic proteinases and peptidases, with photographs of the crystals, will be found in the monographs of Northrop<sup>61b</sup> and Tauber.<sup>80</sup>

It is customary to refer to the sum of the protein-digestant principles in pancreatic juice as "*trypsin*," and that is the meaning of the term as usually employed for clinical purposes, even though Northrop and Kunitz<sup>61a</sup> have applied the term in a more restricted sense to one of the two highly

active proteinases which they were able to extract from animal pancreas in crystalline form.

A diversity of *methods* are available to the investigator desirous of measuring the activity of protease preparations. Tauber<sup>80</sup> speaks of the following general approaches: the increase in amino groups (in the substrate); the increase in the COOH groups; the manometric estimation of amino nitrogen; the Kjeldahl method for non-protein nitrogen; the estimation of residual protein nitrogen; the change in viscosity of protein solutions; milk clotting; the liberation of tyrosine from hemoglobin. In their approach to the trypsin activity of children's duodenal juice Andersen,<sup>6</sup> Shwachman *et al.*,<sup>74</sup> and Kajdi and Davison<sup>48</sup> employed a viscosimeter with gelatin as substrate. Klumpp and Neale,<sup>50</sup> and Philipsborn *et al.*<sup>65</sup> measured the amount of soluble nitrogen liberated from a casein substrate. Andersen and Early<sup>7</sup> recently recommended a modified Fermi method. This is based upon the property of gelatin to no longer solidify at refrigerator temperature after being enzymatically hydrolyzed beyond a certain point. By preparing serial dilutions of duodenal fluid it is possible to measure in roughly quantitative terms the quantity of trypsin contained in a unit volume of duodenal juice. Both Andersen and Early,<sup>7</sup> and Shwachman *et al.*<sup>74</sup> found a close and reliable correlation between results yielded by this simple gelatin-dilution technique and the more elaborate viscosimetric approach.

It may be stated, on the basis of published results, that while one finds wide variation in the trypsin content in fasting secretion among *normal* individuals no significant trend of change has been observed with relation to age.<sup>6,26,48,50,65</sup> Even the 3 premature infants studied by Farber *et al.*<sup>26</sup> had values within normal limits. *Celiac disease* patients showed no significant diminutions in duodenal trypsin.<sup>6,26,65</sup> Infants with *marasmus* exhibited low trypsin activity.<sup>6c,65</sup>

In *cystic fibrosis of the pancreas*, all authors<sup>6c,25a,26,65,94a</sup> described complete or nearly complete absence of duodenal trypsin. Andersen<sup>6c</sup> advised to rely primarily on the assay of trypsin in making a diagnosis of this disorder. She pointed out that duodenal amylase is normally low in early infancy and may be extremely low in the presence of chronic diarrhea without pancreatic fibrosis. Furthermore, the swallowing of saliva, especially when gastric acidity is low, may produce deceptively high results in cases of pancreatic deficiency. For technical reasons the assay of lipase is less reliable than that of the other 2 enzymes. Moreover, low lipase figures have been obtained for a number of patients with other disorders. In no instance, however, in her experience, had trypsin been absent from the duodenal juice of an infant or child without pancreatic deficiency. The low values found in association with extreme *marasmus* were above any that were found in cases of pancreatic fibrosis, and a second determination after clinical improvement was reassuring. Assay of trypsin in the duodenal juice is therefore the most reliable enzymatic means of diagnosing pancreatic deficiency.

**The Bile.** In chemical constitution the bile in healthy childhood appears to run more or less parallel to that of the normal adult. Geptner's analyses,<sup>35</sup> cited by May, indicate that in infancy a random specimen of bile will contain (in round numbers): water 93%, mucin 1.5%, sodium glycocholic acid 2%, sodium taurocholic acid 1%, cholesterin and other lipids 2%, mineral salts 0.5%. Sobotka<sup>78a</sup> has commented on the limited worth of quantitative analyses of bile. Great fluctuations occur in the proportion of various constituents with specimens secured in gall bladder



drainage as well as with human fistula fluid. During and after a period of active hepatic secretion the composition of the gall bladder bile will approach that coming directly from the liver, whereas during stasis the relative content of solids will increase due to absorption of water and salts through the gall bladder wall. It is impossible to obtain reproducibly uniform conditions for the repeated withdrawal of specimens from the same or different individual subjects. Dissimilar methods of analysis also give rise to discordant results, especially with the various pigments and bile acids. For a review of the chemical and biologic literature on bile up to 1937, the reader is referred to Sobotka's<sup>78a</sup> detailed monograph. Agents such as bile salts themselves, which stimulate secretion by the liver, are called *choleretics*, whereas magnesium sulfate and fatty meals which cause emptying of the gall bladder are *cholagogues*. *Anti-choleretics* and *anti-cholagogues*, chiefly pharmacologic substances, exert the opposite effects.

In children, just as with adults, specimens of bile for examination can be readily procured by introducing a tube into the duodenum and injecting a few cc. of a 25% magnesium sulfate solution, or cream, or olive oil. Zelditch *et al.*,<sup>97</sup> Lowenberg and Mitchell,<sup>52</sup> Melamed,<sup>55</sup> Gallerani<sup>34</sup> and other clinical investigators all report that the three "types" of bile—*A*, *B* and *C*—make their appearance in successive order, just as with adults. *A* bile, golden-yellow, is supposed to come from the common duct; *B* bile, darker, more viscous and more abundant, presumably derives from the gall bladder; and *C* bile, clear, light yellow, and of low specific gravity, is assumed to be freshly secreted bile from the liver. Zelditch, Wurmman, Jolkver and Wunditch<sup>97</sup> present the following values for the biliary drainage of children: specific gravity, 1.018 to 1.033; quantity of *B* bile (in  $\frac{1}{2}$  hour or before the appearance of *C* bile), 25 to 40 cc.; bilirubin, sufficiently abundant to be detectable up to dilutions from 1:100 to 1:800. They noted that color in bile specimens runs more or less parallel to the quantity of contained bilirubin.

The bile salts and other *surface tension* reducing substances present in the bile aid the digestive processes by adsorption onto the colloidal interfaces of the chyme-enzyme mixture and alteration of the electrostatic equilibria there present. The surface tension (dynamic) of the duodenal contents of 10 fasting infants was found by Kajdi and Davison<sup>48</sup> to be fairly constant, with a mean of 0.459, and extremes of 0.434 to 0.484. These values were determined by the stalagmometer method, and were expressed as ratios relative to water. Sobotka<sup>78a</sup> concluded that bile increases the efficiency of pancreatic lipase, by both maintaining a favorable environmental pH and specifically activating the enzyme itself. With other enzymes such as amylase and trypsin, bile seems to accelerate enzyme action in a non-specific fashion, probably by virtue of its buffer capacity.

With *infants receiving milk* both Schiff *et al.*,<sup>73</sup> and Müller<sup>58</sup> have observed that the bilirubin coloring of the duodenal secretions begins to fade by 15 minutes after the milk is introduced into the stomach, and is usually completely absent 15 minutes after that. Obviously entry of bile into the duodenum has temporarily ceased. Return of color becomes noticeable 1 to 1½ hours after the feeding, more or less coincident with the stage of recovery from the post-prandial dip in intra-duodenal pH. Schiff postulated that the increased acidity evidenced by the lower pH caused a spasm of the sphincter of Oddi with a transient obstruction to the outflow of bile, but Müller was unable to establish any close correlation between

acidity strength within the duodenum and presence or absence of bile therein. The exact mechanism of this non-stimulating or anti-cholagogue phenomenon merits further exploration. It is not impossible that one reason why a meal of milk fails to call forth any bile rests upon the fact that milk curdles in the stomach before being discharged through the pylorus.<sup>94b</sup> In curdled milk the cream globules are trapped within the mesh of coagulum; hence no fat lies free in the whey to mingle with the duodenal secretions and stimulate the outflow of bile.

Zelditch *et al.*<sup>97</sup> suggest that *cholecystitis* is more prevalent than generally appreciated, and recommend biliary drainage for all cases of obscure abdominal pain, whether acute or recurrent. They described 34 instances of *cholecystitis* encountered at their clinic in Kiev, in children between 6 and 16 years of age. Five were acute, whereas 16 had had symptoms 1 to 4 years. Fourteen were found due to *lamblia* infestation. All patients exhibited abnormal biliary returns, which established the diagnosis. Except when *giardia* was present repeated drainages usually brought the bile back to normal, with concomitant relief or amelioration of symptoms. Inflammatory changes—excessive mucus, floccules, leukocytes, parasites and crystals of cholesterol—were usually present in both the *A* and *B* fractions. Only rarely was the *A* bile normal when the *B* bile was inflamed. When the *C* bile was altered also, as happened often, this was interpreted as meaning involvement of the hepatic passages as well as of the gall bladder and its duct. Lowenberg and Mitchell<sup>52</sup> reviewed the subject of childhood *cholecystitis*. In 1 of their patients biliary drainage was applied with satisfactory results in diagnosis and treatment; in another, the diagnosis was established by this procedure and confirmed later by operation. Melamed<sup>55</sup> described the findings in 32 children aged 3 to 14 who were subjected to duodenal drainage as an approach to the diagnosis of their complaints of abdominal pain. Five were found to have inflammatory changes in the biliary fluid similar to those noted by Zelditch *et al.* and 12 yielded *giardia lamblia* in abundance. The cases diagnosed as having inflammation of the gall bladder and bile ducts were treated by means of repeated duodenal drainage, using magnesium sulfate solutions and peptone cholagogues, "with excellent results."

Gallerani<sup>34</sup> presented 7 cases of what he termed *catarrhal anicteric angiocholitis*. All patients were girls of pre-puberty age, and all had recurrent upper abdominal pains restricted to or most intense in the upper right hypochondrium. On duodenal drainage their specimens yielded coagulated bile, mucus, cholesterol crystals, epithelial cells and abundant numbers of leukocytes occurring singly and in clumps. Inasmuch as these inflammatory findings were always demonstrable in *C* bile, but not constantly present in the *B* bile, Gallerani felt justified in diagnosing inflammation within the hepatic duct system as the primary cause of the symptoms.

For years it has been known that *Giardia lamblia* may infest the duodenum and upper jejunum in myriad numbers. Yet it is surprising to note how few clinical discussions of giardiasis have appeared, in view of the growing recognition of the pathogenicity of this protozoan and its great susceptibility to atabrine therapy. Smithies,<sup>78</sup> who in 1928 reviewed the subject of *giardia* infestation, had described how with adults these parasites may give rise to duodenitis, *cholecystitis* and ulcerative colitis and ileitis. He could usually recover the parasites from the gall bladder when patients who had previously exhibited the parasites in duodenal drainage were subjected to operation,

Melamed<sup>55</sup> treated 12 giardiasis children with small doses of an acridine derivative (Sostol) for 3 days. All cleared completely. In several of these cases the protozoa were demonstrable on duodenal drainage, yet the stool examinations were negative.

Maris and Bushong<sup>54</sup> reported on some 86 children infested with giardia. All were 12 years of age, 74 being below 9 years (50 males and 36 females). The duodenal juice was examined in 9 of 81 cases having positive stools and always found to be positive; 5 other children showed negative stools, but nevertheless had parasites demonstrable by duodenal intubation. The most common complaints were abdominal pain, anorexia, failure to gain weight, nausea and vomiting. Some 50% had from 2 to 24% eosinophils in the differential white blood count. Most of the cases were cured by treatment with atabrine, in dosages from 45 mg. twice daily for the 2 to 4 year olds, up to 90 mg. thrice daily for those 9 years old and upward, over 3 successive days, followed 48 hours after the last tablet with a small dose of magnesium sulfate. One week after treatment, of the 44 children who reported back, 39 no longer suffered from their original primary complaints. The duodenal contents of the first 27 children were examined after the course of treatment and found free from giardia.

Indirect evidence that the duodenal lipase is normal in giardiasis is given by Véghelyi,<sup>84</sup> who studied the digestion and absorption of fat in 14 children having this condition. With 10 of these children the fat content of the dried feces was greater than 20% of the fat ingested, indicative of impaired absorption of this food material. Interestingly, though, more than 60% of this unabsorbed fat was in the form of free fatty acids (normally only about one-fifth of the excreted fat is in the free form<sup>45</sup>). This high percentage of split fat, coupled with the finding that the actual lipolytic activity of the feces of all the patients was normal when tested enzymologically, was interpreted as meaning that there was no deficiency of fat-splitting ferments in the pancreatic and intestinal secretions.

**Internal Secretions of the Duodenum.** Physiologists have demonstrated conclusively that properly prepared extracts of the duodenal and jejunal mucosa contain principles which when injected intravenously act to provoke or inhibit functional activities of other portions of the gastrointestinal tract. These principles must reach their receptor parts through the blood stream if they are to be effective; local application or injection are unproductive of results.

*Secretin*, the first-discovered and best known of these hormones, stimulates the production of fluid and bicarbonate by the pancreatic acini, and enzymes only moderately. Moderate stimulation of bile and intestinal juice is also induced. Purification to the point where a uniform crystalline salt can be isolated—secretin picrolonate—has been announced by Greengard and Ivy.<sup>40</sup>

From the mucosa of the upper small intestine—the same source that yields secretin—of pig, dog and cat, Harper and Roper,<sup>43</sup> and Greengard *et al.*<sup>39</sup> have recovered a substance which when injected intravenously into cats causes a marked increase in the formation of amylase, trypsin and lipase, without augmenting the output of the inorganic constituents. This hormone, which has been named *pancreozymin*, can be separated from secretin by chemical means, and is distinct from it.

The duodenal and upper intestinal mucosa of hogs and other animals contains another specific hormone, *enterogastrone*, which when injected parenterally inhibits the motility and secretion.<sup>38</sup> The secretion becomes reduced not only in volume, but in HCl and pepsin strength as well.<sup>42</sup>

Cursory mention may be given also to *enterocrinin* (Nasset<sup>60</sup>) which seems to elicit secretion from Brunner's glands and succus entericus from the jejunum and ileum; to *cholecystokinin* (Ivy<sup>46</sup>) which seems to induce gall bladder evacuation; and to *villikin* (von Kokas and von Ludány<sup>86</sup>) which stimulates movements of the intestinal wall and may be hypofunctioning in celiac disease.

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## GYNECOLOGY AND OBSTETRICS

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## THE Rh FACTOR IN PREGNANCY

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AMONG the perplexing problems which face the medical profession is that of transfusion reactions. The giving of blood is no longer a compli-

cated procedure reserved only for the most critical emergencies, but now is administered as soon as a patient's condition warrants such additional supportive therapy. With an increase in the number of transfusions, various types of reactions are being recorded. The type of reaction varies from the mild reaction, where a slight chill and fever occur, to the very severe ones, characterized by chill, fever, hemoglobinuria, jaundice, oliguria, convulsions, and occasionally death.<sup>3,21</sup>

Excluding reactions due to faulty administration, incorrect typing or cross-matching, accidents occur in two groups of patients. One group consists of persons who have received repeated transfusions at short intervals. The other group consists of pregnant women who have developed a reaction on the first transfusion. In this latter group some patients, at subsequent pregnancies, have given birth to jaundiced infants, diagnosed as having erythroblastosis. Although many investigators have studied transfusion reactions for years, it is only recently that any really significant discoveries have been made.

Landsteiner in 1901 described the well-known blood groups designated as A, B, AB, and O. In 1927 Landsteiner and Levine discovered a new series of factors, the M and N factors, which are independent of the above groups. They occur individually or in combination with each other, and assist greatly in the exclusion tests of paternity. No anti-M or anti-N agglutinins normally occur, so they have no importance in the problem of blood transfusions.

It is now accepted that many transfusion reactions occurring in pregnancy or the postpartum period are due to the development of Rh antibodies in Rh negative women who are carrying or have recently carried Rh positive children. It is these Rh positive and Rh negative factors which will be discussed in this paper.

**History.** The essential facts which have been discovered in the past few years concerning the Rh factor are as follows:

In 1932 Diamond, Blackfan and Baty<sup>7</sup> were the first to suggest that erythroblastosis fetalis could be divided into three separate syndromes consisting of universal edema of the fetus, icterus gravis, and anemia of the newborn. A critical analysis of 20 cases suggested they were all closely related.

In 1940 Landsteiner and Wiener<sup>15</sup> reported a new agglutinable substance, designated as Rh, of human blood unrelated to the other agglutinogens. This property was designated as Rh because it was detected first with the aid of an immune serum prepared by injecting the blood of rhesus monkeys into rabbits. Those individuals whose blood contained the antigen and would react with the rabbit serum were considered Rh positive, while those whose blood failed to react were considered Rh negative.

The Rh factor differs from the M and N factors in that it produces anti-Rh agglutinins, whereas the M and N factors do not produce anti-agglutinins. Therefore it is related to blood transfusions and their various reactions where the M and N factors are not.

Later in 1940, Levine<sup>18</sup> found atypical isoagglutinins in 5 patients. These had the unique property of greater activity at body temperature than at lower temperatures. In 1 patient the agglutinin apparently resulted from the antigenic stimulus of repeated blood transfusions, while in the remaining 4 individuals the reaction accompanied complications of pregnancy such as repeated miscarriages and death of the fetus. It was assumed that in these latter cases the warm isoagglutinins resulted from immunization of the mother by certain dominant, agglutinable substances in the fetus, and that these agglutinable substances are inherited from the father. The agglutinins showed a specificity which differed from

that of the anti-M and anti-N factors, and tests made on the agglutinin from one serum showed it to be similar to that of the anti-Rh factor of Landsteiner and Wiener.

Levine and Katzin<sup>18</sup> in 1940 noted in some pregnant women the development of isoimmunization after transfusion. The sera of these people showed atypical warm agglutinins at 37° C., which corresponded in specificity to the anti-Rh of Levine and Wiener. The antibody acted on the cells of the husband, lending the support to the theory that under certain conditions a mother may be immunized by her fetus.

The work of Landsteiner and Wiener<sup>16</sup> by 1941 led to the belief that the Rh factor was inherited as a simple Mendelian dominant and is not sex-linked. It involves pairs of the allelomorphic genes Rh and rh, with the Rh being dominant over rh (Rh negative). Both the genotypes Rh Rh and Rh rh will be Rh positive.<sup>22,27</sup>

By 1942 Davidsohn and Toharsky<sup>4</sup> found that the Rh factor was composed of several fractions, and that the Rh antigen in most human blood was not identical with that found in the blood of rhesus monkeys.

Race and Taylor<sup>24</sup> in 1943 discovered a factor in the serum of an Rh positive mother of an erythroblastotic infant, which factor reacted with Rh negative blood and with heterozygous Rh positive blood. This was the beginning of the separation of the genotype of Rh negative persons in order to determine whether they were homozygous or heterozygous.

In 1943 Levine<sup>17</sup> found that isoimmunization is induced by other factors in human blood such as A, B and "Hr" (anti-Hr is Levine's designation for an atypical agglutinin seemingly related to the Rh factor, and found in an Rh positive mother who had borne an erythroblastotic infant). The Hr serum is gotten from an Rh positive mother who has had an Rh negative child. This serum is important in two respects. First, it is useful in checking the existence of an Rh negative factor. Second, it helps in the separation of certain gene types in order to determine if the husband is heterozygous. This factor is identical with the agglutinin described by Race and Taylor above.

In 1944 A. S. Wiener<sup>28</sup> carried out tests on a number of patients with erythroblastotic babies where the usual tests for anti-Rh agglutinins were unsuccessful, and in most cases clean-cut blocking reactions were obtained. This proved the presence of a special sort of anti-Rh isoantibody. The reaction is due to an antibody that becomes fixed to the test cells from which the supernatant fluid has been removed before the anti-Rh test serum was added.

**Occurrence.** The Rh factor is an antigenic substance present in the red blood cells of 85% of the white population of the United States<sup>1</sup> and England.<sup>10</sup> It is absent in 15%, and such individuals are classified as Rh negative. According to Levine, the Rh factor differs in its incidence in the white and colored races. There are 15% of Rh negative white individuals in contrast to only 5 to 8% of colored persons. The condition is rare in the Chinese race. Of 150 Chinese persons tested in New York City, only 1 was found to be Rh negative.<sup>19</sup> Invernizzi<sup>11</sup> states that the percentage of Rh positive factors in South America is "greater in mestizo people, Indians and colored people, than in the white people." The proportion is from 93 to 99% in the former and only 85% in the latter. Landsteiner<sup>14</sup> studied the erythrocytes of 120 full-blooded American Indians and 155 Indians of mixed ancestry for Rh agglutinogens. The blood of only 1 of the 120 full-blooded Indians lacked this factor. In the Indians of mixed parentage the incidence of Rh negative individuals was half way between that found in white persons and in full-blooded Indians.

**The Detection of the Rh Factor.** The presence of the Rh factor is determined by placing a suspension of erythrocytes in 0.01 cc. of a 2% isotonic solution of sodium chloride with 0.02 cc. of anti-Rh serum in a test tube for 1 hour in a water bath at a temperature of 37° C. Fresh blood is used since the agglutinating ability of the Rh factor in the erythrocyte is easily lost. A positive reaction is shown macroscopically by the presence of rugosities around the border of the globular sediment in the test tube. This gives the sediment in the bottom of the tube a rough appearance. A negative reaction is indicated by a smooth sediment in the bottom of the test tube. Upon agitation, clumping of the red blood cells is visible grossly; and this finding always should be checked by microscopic examination.<sup>8</sup>

There are five main factors associated with the Rh factor which are universally designated as Rh<sub>1</sub>, Rh<sub>2</sub>, Rh<sub>0</sub>, Rh', Rh". The three anti-sera used in all testing are therefore known as anti-Rh', anti-Rh", and anti-Rh<sub>0</sub>. The cells that are agglutinated specifically by these sera are called respectively Rh', Rh", and Rh<sub>0</sub>.<sup>26</sup>

In the same way as it is possible for agglutinogens to pass from the fetal to the maternal circulation, it is possible also for the Rh antibodies, formed in the maternal blood, to leak back into the fetal circulation and thus produce erythroblastosis fetalis. This condition is characterized by the presence of numerous nucleated red cells in the fetal circulation. The widespread persistence of extramedullary hematopoiesis is the response of the body to an excessive loss of red cells, and the occurrence of immature red cells in the circulation discloses the inability of the body to provide a sufficient number of mature cells. Furthermore the leakage of Rh agglutinins from the maternal into the fetal circulation leads to a continuous destruction of fetal red cells. During neonatal life the agglutinins present at birth continue their work until they are exhausted. If the infant is tided over this period by transfusions of Rh negative blood, the destruction of red cells will cease and its condition will become relatively normal.

Witebsky *et al.*<sup>30</sup> tested red blood cell suspensions from blood clots of 9 individuals of Group O against: (a) guinea pig immune serum, (b) serum of a mother of an erythroblastotic infant, and (c) breast milk from the mother. They found that blood specimens which were Rh positive with guinea pig's immune serum and with the patient's serum were also positive when tested against the milk. They concluded, therefore, that the milk contained the same Rh antibody as the blood serum. In a further study, Witebsky and Heide<sup>29</sup> found Rh antibodies in the breast milk of 2 mothers who recently had delivered erythroblastotic infants.

**Erythroblastosis Fetalis.** Macklin<sup>20</sup> defines erythroblastosis fetalis as a condition in which the blood of the fetus exhibits immature cells of the erythrocytic type which are not normal as to either type or quantity for the stage of development of the fetus. She assumes that hemolytic disease of the newborn, as well as erythroblastosis fetalis, is due to other factors than hemolysis. If fetal erythroblastosis is due to an antigen-antibody reaction, hemolysis will occur with accumulation of iron in the fetal liver and with persistent extramedullary hematopoiesis. This is known as hemolytic disease of the newborn and is usually due to the Rh factor complex.

The typical picture of erythroblastosis fetalis is that of jaundice appearing soon after birth, enlargement of the liver and spleen, and other symptoms. These may include varying degrees of any of the following conditions: somnolence, listlessness, and flaccidity; muscular twitchings, opisthotonos, and occasional convulsions; vomiting and diarrhea; petechiae,



ecchymoses, bleeding from mucous surfaces, increased bleeding and coagulation times; edema, cyanosis, and respiratory difficulties; and collapse. In addition, a large number of circulating immature red blood cells (normoblasts and erythroblasts), a leukocytosis, an eosinophilia, or a monocytosis may be present. The hemoglobin percentage and number of red cells are reduced, but the color index is above normal.

The child may appear strong and vigorous at birth, but symptoms may appear very soon. Death may occur within a few hours or days, but occasionally not until the 2nd or 3rd week. Several erythroblastotic infants have been described whose deciduous teeth were deeply discolored with a grayish-green pigment which seemed to be incorporated in the deeper layers of the teeth rather than merely upon their surface. This discoloration probably was a part of the erythroblastotic process, caused by an excessive deposit of blood pigments during the prenatal formation of the enamel and dentine.

Erythroblastosis fetalis has been classified into three distinct entities: (a) congenital anemia; (b) icterus gravis, and (c) fetal hydrops. Congenitally anemic infants, as a whole, have a very mild anemia at the onset which slowly becomes severe; the other two types also show a great degree of anemia from birth. The icterus gravis group is most likely to show a hemorrhagic tendency; the hydrops infants are universally severely damaged. All three groups exhibit splenomegaly and hepatomegaly. Congenital anemia is the least severe form of erythroblastosis, while hydrops is the most severe. The majority of the simple congenital anemia group recover following adequate treatment; a smaller percentage of the icterus gravis group survive; but none of the hydrops infants live. It is interesting to note that the same mother may give birth to infants manifesting any one of the three forms of the disease. The usual sequence is to find a progression in the severity of the disease as the number of pregnancies increases. The first erythroblastotic child may suffer from the congenital anemic form, the next may have icterus gravis, and the third may be a hydrops case.

As stated by Davidsohn,<sup>5</sup> there are four conditions which determine the severity of fetal erythroblastosis and the place where it appears in a family:

1. The age of the fetus when Rh antibodies begin to act on it.
2. The length of time the fetus is exposed to these Rh antibodies.
3. The strength of the Rh antibodies. The titer of anti-Rh agglutinins in the blood of the mother may or may not be a measure.
4. The permeability of the placenta. There may be quantitative differences of permeability in women. The permeability of the placenta may vary at different times during pregnancy.

The characteristic gross and microscopic changes in the placentas of mothers of erythroblastotic infants have been described by Hellman, Hertig and Javert.<sup>12</sup> The placentas may reveal hematomas which contain numerous normoblasts and erythroblasts most likely of fetal origin. Such placental lesions provide for the transmission of the Rh agglutinin from the fetus to the mother. This results in isoimmunization of the latter.

Yannet<sup>31</sup> observed that certain children who had recovered from icterus gravis subsequently exhibited evidence of central nervous system injury. This included severe mental deficiency, extrapyramidal spasticity and athetosis. A necropsy on 1 of these children confirmed the relationship of the cerebral changes originally described as kernicterus with the aforementioned clinical picture.

Since Rh isoimmunization is important in the etiology of erythroblastosis

fetalis, and since kernicterus is found primarily in children with erythroblastosis, it would appear that the cerebral changes which occur in association with kernicterus may in some way be related to the Rh factor. Yannet suggests that certain cases of imbecility and idiocy now classified as of unknown etiology may arise as the result of Rh isoimmunization of the parent. In an unselected group of women with unclassified mentally deficient offspring approximately 25% were Rh negative. Among an equal number of mothers of Mongolian, diplegic and microcephalic children the incidence of Rh negative blood was in the normally expected range of about 12%. Although the total number of deficient children examined to date (approximately 100) is not large enough from which to draw definite conclusions regarding the relationship between erythroblastosis fetalis and mental deficiency, the results are of sufficient interest to warrant a further study of this subject.

**The Occurrence of Erythroblastosis Fetalis.** Erythroblastosis fetalis afflicts the offspring of about 1 in 400 mothers who are Rh negative.<sup>12</sup> Potter<sup>23</sup> states that about 12% of marriages are between Rh negative women and Rh positive men; and, although erythroblastosis fetalis is possible in the offspring of 12% of marriages, it occurs in only 0.1% of marriages. Schwartz and Levine<sup>25</sup> noted among 152 consecutive stillbirths and neonatal deaths, an incidence of erythroblastosis of 4.4 to 8.2%. Javert<sup>13</sup> found that 92% of mothers of erythroblastotic infants are multiparas and that the incidence of erythroblastosis varies with the parity. For example, the incidence of erythroblastosis fetalis in families in which the disease appears for the first time, in the second child or later, is about 50% for the second and subsequent pregnancies; whereas, if the first-born had the disease, nearly 100% of the subsequent ones suffer from it.<sup>12</sup>

At the Hospital of the University of Pennsylvania among 836 consecutive registered ward cases there were 60 Rh negative mothers; but only 4 of these patients gave birth to erythroblastotic infants, an incidence of about 6.4%. Among the 60 tested husbands of these 60 Rh negative wives, only 5 were found to be Rh negative. Table 1 shows these 4 cases of erythroblastosis fetalis and the order in which they appear in each family.

TABLE 1.—INCIDENCE OF KNOWN TRANSFUSION REACTIONS AND OF ERYTHROBLASTOSIS AMONG 60 COUPLES IN WHICH THE MOTHERS WERE RH NEGATIVE

Family ident. No.	Mothers			Infants		
	Age	Present parity	Transfusions	Erythroblastosis		
				Birth order	Form	Survival
1	30	VII	5th pregnancy—severe reaction	6	Icterus	No
				7	H.E.	Yes
2	31	X	7th pregnancy—mild reaction	8	H.E.	Yes
				9	H.E.	Yes
				10	Icterus	No
3	38	III	None	3	H.E.	Yes
4	29	II	None	2	H.E.	Yes

H.E.—Hemolytic anemia.

Note that the 2 mothers who had transfusions experienced untoward reactions to this type of treatment and that both of these women gave birth to erythroblastotic infants in their subsequent pregnancies.

It can be seen, therefore, that the mere presence of the Rh negative factor in the woman and the Rh positive factor in the man are not always sufficient to result in erythroblastosis in the offspring. Some of the following explanations have been offered:

1. Due to the small size of many families, the chance of isoimmunization by successive pregnancies is reduced.
2. Variation in the permeability of the placenta of different individuals may influence the passage both of the Rh positive factor from the fetus to the mother and of specific antibodies from mother to fetus.
3. The ability of Rh negative women to produce immune anti-Rh agglutinins, in response to the stimulus of Rh positive cells, is variable.
3. The disease may occur in mild form and not be recognized.
4. Many males are heterozygous and therefore do not transmit the factor to all children.

**Treatment of Erythroblastotic Infants.** Treatment depends entirely on the condition of the infant at the time of delivery. If the child is apneic and cyanotic, intratracheal or intranasal oxygen is administered. A red blood count is taken immediately; and, if it is 3.5 million or more, no transfusion is given. The count should be repeated daily. If it does not drop during the next 5 days, no transfusion is required. However, if the original count is lower than 3.5 million or drops during the succeeding days, transfusions of Rh negative blood should be given.<sup>2</sup>

Gimson<sup>9</sup> has shown that the transfusion of Rh negative blood is better than that of Rh positive blood. Hemolysis of the patient's red cells is not prevented by giving Rh negative blood, but blood is being provided which will not be destroyed more rapidly than normally. The infant can live, by receiving such transfusions, until the hemolytic process of the disease has come to an end. Rh negative erythrocytes are known to survive at least 90 days, whereas Rh positive ones are destroyed within a few days of transfusion. The amount of blood used for transfusing these small infants was calculated by Gimson as follows:

$$\frac{\% \text{ rise of Hb required}}{100} \times \text{blood vol.}$$

The amount of blood is usually around 60 cc., and the number of transfusions varies from 2 to 6.

**Heterozygous vs. Homozygous Parentage.** Males who have inherited the Rh factor from only 1 parent are heterozygous and, therefore, do not transmit this factor to all of their offspring. The children who do not inherit the Rh factor escape erythroblastosis fetalis. Most fathers of erythroblastotic infants are homozygous. This fact reduces considerably the possible incidence of the disease since only about 43% of all Rh positive persons are homozygous. It is only recently that it has been possible to determine whether the father is heterozygous or homozygous.

In order to make this distinction the red blood cells of the father are set up against the three standard Rh sera—Rh', Rh'', Rh<sub>0</sub>—and also the Hr serum. If the father's cells are agglutinated by Rh' and Rh<sub>0</sub> serum but not by the other 2, he is homozygous. He will not have any negative genes to pass on if his cells are agglutinated in Rh', Rh'', and Rh<sub>0</sub> sera. If his cells are agglutinated in Rh', Rh<sub>0</sub>, and Hr serum, he is probably heterozygous but may belong to a rare subgroup of the Rh series. He will be heterozygous also if his cells are agglutinated in Rh<sub>0</sub>, Rh'', and Hr serums, unless he again belongs to one of the rare subtypes.

There are some additional aids which help in this diagnosis. For

example, if an Rh negative mother and an Rh positive father have an Rh negative infant, the father probably will be heterozygous. If either parent of the father is found to be Rh negative, the father undoubtedly will be heterozygous.

**The Agglutinating and the Blocking Antibodies.** As soon as a pregnant woman is discovered to be Rh negative, it is important to test for the presence of antibodies in her blood. These may exist either as agglutinating or blocking antibodies; the presence of the latter gives a much poorer prognosis for the fetus than the presence of the agglutinating antibody. Serial dilutions of the mother's serum are tested against the cells which she agglutinates. The presence of agglutinins is found by titrating against the cells most strongly agglutinated by the above procedure. The presence of the blocking antibody is tested by the method which was recently described by A. S. Wiener.<sup>28</sup> This antibody interferes with the agglutination of Rh positive cells by standard anti-Rh serum.

The finding of agglutinating antibodies in a pregnant woman means that there exists a potential danger to her infant. Titers of her agglutinating antibodies should be made at 6 week intervals during the first 7 months of her pregnancy and at 4 week intervals during the last 2 months. As this titer rises, the danger of erythroblastosis fetalis occurring increases. If the titer drops sharply, it can be assumed with a high degree of certainty that the fetus will be seriously affected. If the blocking antibody makes its first appearance as the titer of the agglutinating antibody falls, a fatal prognosis for the infant can be made in practically every case.

The effect of the agglutinating and blocking antibodies upon the fetus *in utero* depends upon the length of time it is exposed to these antibodies. The longer the exposure the more will be the damage to the offspring. At present some investigators think that the early appearance of a low titer is as damaging to the infant as a sudden rise in the titer in the last few months of pregnancy. The exposure of the fetus to these antibodies can be shortened by a premature delivery by means of Cæsarean section. This should be done at the time when the titer falls and before the blocking antibody appears.

**The Significance of the Rh Factor in Pregnancy.** Knowledge of the Rh factor is important from several clinical points of view. Rh negative women who have, in the course of a pregnancy, developed anti-Rh agglutinins may experience serious transfusion reactions which occasionally may be fatal. These reactions may occur from the first but, more frequently, from subsequent transfusions.<sup>6</sup> For this reason it is important to determine the Rh reaction of every pregnant woman since she may require a transfusion at the time of delivery. Knowledge of the Rh factor is important also because the transfusing of an Rh negative woman with Rh positive blood may initiate the formation of anti-Rh agglutinins and thus induce erythroblastosis fetalis in subsequent offspring. Such children may show varying degrees of hemolytic anemia.

An Rh negative woman should be tested next for the presence of any antibodies she might possess. It is important to determine if such antibodies are of the agglutinating or blocking variety. If the former are found, the titer should be determined and be followed as noted above.

The next step is to discover whether the father is homozygous or heterozygous. If the mother has had a previous erythroblastotic infant and her husband is homozygous and she now possesses agglutinins, she should be advised against having future children. However, if her husband is heterozygous, there is a better chance that normal infants may result.

At the present time we have no method for preventing the development of erythroblastosis fetalis, but experience to date has supplied us with certain useful information. First, it is known that we can avoid sensitizing mothers who are Rh negative by transfusing them always with Rh negative blood. Second, we can predict with a relative degree of accuracy the health of offspring to be born to parents whose Rh factors differ. With such knowledge preparations for the proper treatment of the mother and child can be made in advance.

Prevention of erythroblastosis fetalis can be sought only in prophylactic directions, and may be so important to the parents as to be considered in some instances. Prevention of subsequent pregnancies by sterilization is to be considered. Also, it has been suggested that individuals prior to marriage should be tested for their Rh factor so that they may be warned in advance of the type of offspring which may result from such unions. Artificial insemination might be discussed with persons whose infants all have had erythroblastosis, but who are strongly desirous of having normal children. Therapeutic abortion also should be considered where investigation has shown that it would be unlikely for the mother to deliver a normal infant. This should be considered because the mother is not wholly without danger while carrying a sensitized infant. It has been shown also that late abortions and abruptions of the placenta occur unusually frequently in these cases.

**Summary.** 1. Blood transfusion reactions may occur in persons whose blood has been properly typed and cross-matched, but who receive blood of the wrong Rh type.

2. Most blood transfusion reactions in Rh negative individuals can be prevented by transfusing them always with Rh negative blood.

3. An Rh negative pregnant woman may be sensitized either by a transfusion of Rh positive blood or by carrying an Rh positive fetus. In such an event the infant is very likely to suffer from erythroblastosis fetalis.

4. If an Rh negative pregnant woman possesses both agglutinating and blocking antibodies in her serum and her husband is homozygous, great consideration should be given to the advisability of interrupting her pregnancy because of the added dangers to herself and the unlikelihood of having a normal, healthy infant. Future pregnancies also should be advised against in this case. If no agglutinins are present and her husband is heterozygous, there is a 50% chance that her infant will be normal.

5. The incidence of erythroblastotic infants born at the Hospital of the University of Pennsylvania to 60 couples in which the mother was Rh negative and the father Rh positive in 1 year was 6.4%.

6. Many infants suffering from hemolytic disease of the newborn can be saved if the occurrence of the disease is foreseen, its existence recognized at once, and the infant transfused with Rh negative blood when needed.

7. Erythroblastosis fetalis can be prevented by: (a) knowledge of the couple's Rh factor before marriage, (b) artificial insemination, (c) therapeutic abortion, or (d) sterilization.

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## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 17, 1945

**Factors Influencing the Maintenance of Blood Levels of Sulfonamides.**  
R. H. SILBER and I. CLARK (Merck Institute for Therapeutic Research, Rahway, N. J.). A comparison of the fate of sulfaquinoxaline (SQ), sulfamerazine (SM), sulfadiazine (SD), and 3 derivatives of sulfaquinoxaline was made in rats after administration of single doses of 200 mg. per kg. orally or intravenously. Blood and plasma levels, liver levels, gastro-intestinal content, urinary and fecal excretion, and binding by plasma protein were determined.

Sulfaquinoxaline, an amino derivative (2-sulfanilamido-6-aminoquinoxaline), and an acetyl derivative ( $N_4$ -acetyl-sulfaquinoxaline) were 88.5 to 93.5% bound by rat plasma, compared with 74.5% SM and 62% SD. The 2 derivatives of SQ were removed from the blood as quickly as SM or SD in spite of the high degree of plasma binding. Striking prolongation of SQ blood levels resulted from excretion into the intestine and a delay in gastro-intestinal emptying time. After 24 hours the delaying effect of SQ was confirmed by the presence of 30% of an oral dose in the stomachs of fasting rats, whereas SM and SD had been completely removed. The hydroxy derivative (2-sulfanilamido-3-hydroxyquinoxaline), an insoluble compound, was also retained in the gastro-intestinal tract and after intravenous administration blood levels were prolonged almost as long as those of SQ. It was possible to maintain SD levels as well as those of SQ by withholding food after oral administration of the drug. This was correlated with a decrease in fecal loss and retention of drug in the intestinal tract.

Plasma binding alone cannot account for prolonged blood levels of sulfonamides. Other factors which determine the magnitude and maintenance of blood levels in rats are: (1) solubility in (and absorption from) the intestinal tract; (2) the presence or absence of food; (3) the emptying time of the gastro-intestinal tract; (4) excretion into the intestinal tract; and (5) urinary and fecal excretion.

**Effects Produced in Man by Inhalation of High Concentration of Oxygen for 24 Hours.\*** JULIUS H. COMROE, JR., ROBERT D. DRIPPS, PAUL R. DUMKE and MARGO DEMING (Depts. of Pharmacology and Anesthesia and Harrison Dept. of Surgical Research, Univ. of Penna.). The effects produced by breathing high concentrations of oxygen for prolonged periods of time have been studied by many investigators in a variety of animals and all have reported the occurrence of irritation, congestion and edema of the lungs and even death following long exposures. Similar well-controlled experiments have not yet been done upon large series of men. In the present study 100% oxygen was administered continuously to 34 healthy young males for a period of 24 hours without any intermission. Twenty-eight subjects (82%) experienced substernal aching which was usually made worse by deep inspiration. This substernal discomfort was slight in 4, of moderate intensity in 18, and severe in 6 subjects. The symptoms developed in an average of 14 hours; after the 24 hour period was completed the symptoms gradually decreased over a 4 to 12 hour period. Signs of nose, throat and eye irritation were common. The vital capacity was decreased markedly in a large number of these subjects, the maximal being 1480 cc. in 2 instances. A group of 10 subjects breathing through identical apparatus (full face mask and demand apparatus) but supplied with air rather than 100% oxygen developed no symptoms during the 24 hour period. Another group of 10 subjects breathing 50% oxygen for 24 hours developed no substernal distress. When 75% oxygen was breathed for 24 hours substernal distress was noted in 55% of the subjects. It appears that oxygen in excess of 50% is required in order to produce toxic symptoms in man over this period of time. Breathing of 100% oxygen at 18,000 ft. equivalent altitude for 24 hours produced no symptoms in a group of 6. Since the total oxygen tension in this experiment is equivalent to the inhalation of 50% oxygen at sea level, this indicates that symptoms are due to high oxygen tension rather than to elimination of nitrogen from the body.

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**The Effect of Respiratory Movements Upon the Circulation.** ISAAC STARR and CARL K. FRIEDLAND (Hartzell Research Department of Therapeutics, Univ. of Penna.). The ballistocardiogram regularly shows a respiratory variation. The impacts increase during inspiration and diminish during expiration. If the breath is held this variation disappears. These findings fit with the concept that inspiration increases cardiac output by increasing filling pressure, and they are consistent with the results of animal experiments by Boyd and Patras (1941). However, the respiratory variation of the peripheral blood flow, as suggested by records from finger plethysmographs (Bolton *et al.*, 1936; Burton, 1939; and Burch *et al.*, 1942), was often the reverse of the ballistocardiograph changes, as were blood pressure changes in some of our patients. Also there was a possible alternative explanation of the ballistocardiograph respiratory variation, namely, that it was due to change in position of the heart rather than change of output.

To ascertain whether position or pressure changes caused the ballistocardiogram's respiratory variations, we performed 2 types of experiments. Changing the position of the subject on the ballistocardiograph, to get the direction of recording in line with the cardiac axis at full expiration, *did not* reverse the normal respiratory variation. Also in a patient in

\* Work done under contract with the Office of Scientific Research and Development.

the decerebrate condition after an unsuccessful brain operation positive pressure respiration *did* reverse the normal ballistocardiograph respiratory variation. These findings demonstrate that the respiratory variation is related to pressure changes and not to position.

The opportunity to study the subject further came with the discovery of a patient with ventricular aneurism whose ballistocardiogram showed a doubled J wave. We believe that the first peak was derived from the impact from the normal right heart, while the second was from the abnormal left, which was forced to expand the aneurism before ejection. These 2 peaks had a different respiratory variation, the first increased in height during inspiration while the second diminished.

We also experimented with healthy persons given artificial respiration with blasts of air, while pressure in the mask was recorded by a Frank capsule and chest position by an inflated bag and tambour. In 1 case, arterial pressure was also recorded by a Hamilton manometer.

All our results are consistent with the following hypothesis, an old view given by Bazett (in Macleod's "Physiology in Modern Medicine," 1941) and supported by the experiments of Shuler *et al.* (1943) and Dupee and Johnson (1944). During inspiration better filling increases the output of the right ventricle but the increment first goes to fill the lungs whose blood capacity is increasing as they expand. For the same reason the left ventricle is less well filled during early inspiration and its output diminishes; later, if inspiration is sufficiently prolonged, the wave of increased output from the right side reaches the left and increases its output. During expiration right ventricular filling diminishes, and its output diminishes also. But now blood is squeezed from the contracting lungs into the left side of the heart and its output is maintained or increases.

Healthy subjects with sinus arrhythmia show an interesting phenomenon when given artificial respiration with blasts of air. The slowing of the pulse, normally present during expiration, then appears at other positions of the respiratory cycle, especially during inspiration. Under all circumstances it is the small impacts that are slowed. The heart slows down as if it were waiting to be properly filled before contracting.

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**Treatment of Clinical Hyper-pituitarism With Hypertension by Injections of Pitressin Tannate in Oil.** J. Q. GRIFFITH, JR., N. PADIS, and E. ANTHONY (Robinette Foundation, Hospital of the University of Pennsylvania). Sixty-two patients were studied who had both elevated arterial pressure and a blood serum that was able to delay water diuresis in rats when injected intraperitoneally. There were 33 males and 29 females. Ages ranged from the 2nd to the 6th decade, with only 5 subjects below 30. Period of observation ranged from 3 to 26 months following treatment, the average being 8 months. In all, 63 courses of treatment were given: (1) 13 persons were given injections of aqueous pitressin (Parke Davis) hypodermically, the dose ranging from 0.2 to 1 cc., repeated daily or at longer intervals, for 6 injections or more; (2) 10 persons were given 1 cc. of pitressin tannate in oil (Parke Davis) at weekly or monthly intervals, the number of injections being less than 6; (3) 40 persons were treated similarly, except the injections were 6 or more. Results were definitely better for the last group than for the first 2 groups. However, considering all 3 groups as a whole, systolic and diastolic blood pressures were significantly lowered and clinical improvement occurred in about 50% of



the subjects. This was associated, usually, with disappearance of anti-diuretic substance from the patient's serum. Results could not be predicted on the basis of age or sex, nor from preceding testing of cutaneous lymphatic flow, or capillary elasticity as demonstrated by cutaneous capillaroscopy. No patients were treated who showed evidence of diminished renal function, or had high titers for gonadotropic hormone in serum. Sharp reactions occurred following the injections of the aqueous preparation, but not after the preparation in oil, although 2 subjects showed mild and transient urticaria. Injection therapy was not used in the very elderly and especially not in those with systolic blood pressure much above 200. We, therefore, suggest that repeated injections of pitressin tannate in oil (not aqueous pitressin) offer a form of therapy effective in certain selected cases of hypertension.

# BOOK REVIEWS AND NOTICES

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**THE MARCH OF MEDICINE.** The New York Academy of Medicine Lectures to the Laity, 1944. Pp. 121. New York: Columbia Univ. Press, 1945. Price, \$1.75.

AMONG the many enviable achievements and activities of the New York Academy of Medicine, its series of lectures to the laity, now in its 10th year, is one of the most significant. These lectures aim to reveal to the public the historical and philosophic backgrounds of medicine and public health, and their relationships with the collateral sciences of psychology, sociology, criminology, economics, and even world politics—a considerably larger target than merely to keep the public informed about recent medical discoveries. They are no small tribute to the vision of the Academy's benefactor, Linsley Williams, after whom one of the lectures is appropriately named.

The 6 lectures of the present series are, as usual, all by eminent men and cover an even wider range than cabbages and kings: Morale and Propaganda (E. A. Strecker); Food and Civilization (C. G. King); The Past, Present, and Future of Chemotherapy (C. M. MacLeod); Medicine and the Changing World (R. Fitz); The Effects of Science Upon Human Beings (Sir G. Campbell); and Wars and Epidemics (Lt. Col. T. T. Mackie). The series, labelled by Dr. A. F. Chace, the Academy's president, "War and the Expanding Frontiers of Medicine" gives pabulum to many kinds of mind and taste. Dull indeed is the mind or taste that finds no profit or pleasure in the perusal of this volume of the March of Medicine. E. K.

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**THE COMMON COLD AND HOW TO FIGHT IT.** By NOAH D. FABRICANT, M.D. Pp. 107. New York: Ziff-Davis, 1945. Price, \$1.50.

THIS little book, written by a nose and throat specialist, is a comprehensive survey of all that is currently known concerning the common cold. Though intended primarily for the intelligent layman, the material differs from that which might be found in a medical textbook only in the simplicity and clarity of presentation.

After a preliminary description of the structure and function of the nose Dr. Fabricant surveys our present knowledge concerning the causes, complications, prevention and treatment of the cold. After reviewing the many methods used for treating the cold and indicating their questionable value, the author states that warmth, rest in bed, and the application of moisture to the nose are the sanest techniques available.

More specific therapy will have to await the work of the research man.

M. K.

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**A TEXT BOOK OF PSYCHIATRY FOR STUDENTS AND PRACTITIONERS.** By D. K. HENDERSON, Professor of Psychiatry, Univ. of Edinburgh, and R. D. GILLESPIE, Physician for Psychological Medicine, Guy's Hosp., London. Sixth Ed. Pp. 719. New York: Oxford Univ. Press, 1944.

THIS edition maintains the high standard of previous editions, which, in the Reviewer's opinion, have established the work as the most satisfactory text available in English. In addition to incorporating the important recent advances, the latest edition presents some minor rearrangements of contents. The section on the psycho-neurotic reaction types now precedes that on the

psychoses and all the paranoid reaction types have been grouped together. A chapter on "Special Methods of Physical Therapy" summarizes excellently the present status and techniques of the various shock therapies. A short discussion of the electro-encephalographic findings has been included in the chapter on "Epilepsy." The section on "War Psychiatry," revised and enlarged, presents a basic survey of the problems encountered in this important aspect of Psychiatry. In line with current trends, the social aspects of Psychiatry have been stressed. The general orientation follows the psychobiologic approach of Adolph Meyer.

This book is highly recommended to students, practitioners, and others as a comprehensive, sound, and very readable authoritative text on Psychiatry.

C. R.

**NEURO-OPHTHALMOLOGY.** By DONALD J. LYLE, B.S., M.D., F.A.C.S., Lecturer on Neuro-ophthalmology, Department of Anatomy, Med. Coll. of the Univ. of Cincinnati; Attending Ophthalmologist to the Good Samaritan Hosp., Christ Hosp., Jewish Hosp., St. Mary's Hosp., and Children's Hosp. Pp. 398; 7 charts, 529 ills. Springfield, Ill.: Thomas, 1945. Price, \$10.50.

THIS is a welcome addition to the few monographs in English which deal primarily with Neuro-ophthalmology. It is more of an introduction than a handbook and the graduate student will naturally desire much more information than this book affords.

The illustrations are good and as far as it goes, the text is readable and well documented with case reports. A very excellent bibliography of some 1700 references is given at the end of the book.

F. A.

**THE BIOLOGICAL BASIS OF INDIVIDUALITY.** By LEO LOEB, Professor Emeritus of Pathology, Washington Univ. School of Medicine, St. Louis. Pp. 714; no ills. Springfield, Ill.: Thomas, 1944. Price, \$10.50.

THE purpose of this book is to analyze the foundations of individuality. Two types of individuality are considered: "The first one is the mosaic type which represents the sum of the particular organ and tissue characteristics (organ and tissue differentials) which determine structure, metabolism, motor and psychic activities and the component parts of which differ in different individuals." "The second type of individuality which may be designated as the essential individuality is characterized by the presence of a chemical factor—which is common to the different organs and tissues of each individual and which differs from the corresponding chemical characteristics of the organs and tissues of every other individual."

The book is arranged in 8 parts, with chapter subdivision. Part I, Transplantation of Tissues in Higher Vertebrates, as a Method for the Analysis of the Organismal Differentials. Part II. The Phylogenetic and Ontogenetic Development of Individuality and Organismal Differentials. Part III. The Significance of Organismal Differentials in the Interaction Between Single Cells. Part IV. Tumors and Organismal Differentials. Part V. Organismal and Organ Differentials and the Specificity of Tissue Reactions. Part VI. Organismal Differentials and Organ Differentials as Antigens. Part VII. Organismal Differentials, Organ Differentials and Evolution. Part VIII. The Psychological—Social Individuality.

The material is drawn largely from observations of the host to transplanted tissues from various sources, a field in which the author has published many papers. The Reviewer found the book somewhat difficult to read because of the author's style, but was impressed by the vast amount of material and the sound reasoning employed in its interpretation. The comprehensive bibliography should be of value to workers in almost any branch of biologic investigation. It is difficult to evaluate the book from the standpoint of its contribution to our knowledge of Biology. To the worker who employs transplantation methods the volume holds a wealth of material.

D. C.

**THE PATHOLOGY OF INTERNAL DISEASES.** By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology and Bacteriology in the Univ. of Toronto. Fourth Ed., revised. Pp. 857; 366 engr., 8 color plates. Philadelphia: Lea & Febiger, 1944. Price, \$10.00.

Early in its career this textbook established a well-deserved reputation as the most easily readable of the pathology textbooks. Thus, it soon became a favorite of students. Now it is in the 4th edition and is still going strong.

In this new edition there are no radical changes but a number of important additions have been made. New material includes: the demonstration of collateral coronary circulation by injection, the relation of trauma to coronary disease, disseminated lupus erythematosus, atypical pneumonia, psittacosis, adenomatosis of the lung, blast injury, infectious hepatitis, dietary cirrhosis, alloxan diabetes, intercapillary glomerulofibrosis (sclerosis), nephrosis following incompatible transfusions and crush injury, the pathogenesis of Graves' disease, sarcoidosis, and the importance of the Rh factor in erythroblastosis.

A few sections have been largely rewritten, notably etiology of rheumatic fever, the time factor in coronary infarcts, pyelonephritis, intracranial aneurism, and the pathogenesis of poliomyelitis.

There are several new figures and color plates.

This new edition will undoubtedly maintain its place as one of the leaders among the standard pathology textbooks and can be recommended for both student and practitioners.

W. S.

**THE NEUROLOGIST'S POINT OF VIEW: Essays on Psychiatric and Other Subjects.** By I. S. WECHSLER, M.D. Pp. 251. New York: Fischer, 1945. Price, \$3.00.

THIS author states that the Jew has a neurotic character makeup, and that persisting to be a Jew means to court the possibility of a neurosis; but, he continues: "among all peoples and races whatever progress was made came from men of neurotic makeup, if not with actual neuroses." The prejudices and conflicts which harm our individual lives, and the origins of modern man's difficulties in adjustment are among the important topics discussed; these and other subjects constitute this collection of papers published previously. The chapters are: Nervousness and the Jew; An Inquiry Into Racial Psychology; The Legend of the Prevention of Mental Diseases; The Neurotic Conflict Between the Individual and Society; The Psychology of Anti-Semitism; Anti-Semitism as a Neurosis; Sigmund Freud: a Critical Appreciation; The Problem of Mental Disorders: The Neurologist's Point of View; Maimonides the Physician; Moses and Monotheism: A Review; On Palestinian and Russian Colonization, A Chronicle; A Brief History of Psychiatry.

In regard to Freud, doubt is expressed as to whether objective criticism is yet permissible. While admitting the danger of great generalizations on isolated observations, Freud is said to have possessed the essentials necessary to a scientist or poet—great ingenuity and wide imagination to a hazardous degree. Freud's concept of the unconscious is regarded as his greatest contribution, wherein is visioned "an active, dynamic unconsciousness which is entirely outside the realm of awareness and which, indirectly, is capable of influencing conscious behavior." The "nonsense" of Adler and the "universal consciousness" of Jung are considered outside the realm of psychoanalysis. Freud's fine concept of sublimation has been assailed in "that it does violence to ethical principles and noble ideals to allege that they are rooted in ugly unconscious impulses." Plunging into this controversy, the author says: "Friendship is a beautiful sentiment, even though it be alleged that it is the sublimated result of unconscious infantile homosexuality." Among other conclusions the writer states: "I would venture the guess that analysis will be remembered longest for the insight into normal and abnormal behavior which it has vouchsafed and for its excellence as a method of investigation." Freud's effort to establish Moses as an Egyptian, or to question his

ever having lived, was not pleasing to most Jewish people, nor have his contentions convinced most scholars. That the Jews were the traditional "Chosen People," was accepted by Freud, but he asserts it was Moses who chose them.

N. Y.

CONSTITUTION AND DISEASE. Applied Constitutional Pathology. By JULIUS BAUER, M.D., Professor of Clinical Medicine, Coll. of Medical Evangelists, Los Angeles. Pp. 247. 2nd Ed. New York: Grune & Stratton, 1945. Price, \$4.00.

THE author appears to define "applied constitutional pathology" as the facts of endocrinology and other branches of medicine correlated to the particular situation encountered in individual patients. Yet I can read through large sections of this book without finding any such correlation. Surprise is not limited to the obvious shortcomings in the interpretation, it is equally unexpected to hear from Germanic sources that Americans neglect the patient's whole personality in their concern about laboratory procedures and should give heed to the artistic trend of pre-war Vienna and Paris. It is a poor practitioner, indeed, who would not subscribe to the aphorism "In clinical medicine the laboratory is a good servant but a bad master." The author endorses the general dislike of speculative approach insufficiently supported by facts, yet many statements in a text fall into this error. These of course are serious not fatal shortcomings in a book "intended to familiarize the reader with the principles of constitutional thinking"; and one may say that this aim has been accomplished. Furthermore, numerous examples of the importance of the constitution are to be found and valuable advice offered on such matters as the range of normality. One is glad to find an index to this second edition.

E. K.

THE DOCTOR'S JOB. By CARL BINGER, M.D. Pp. 243. New York: Norton, 1945. Price, \$3.00.

THE layman for whom these essays appear to have been written—or is it perhaps the young medico starting on his career, or the older medico needing to adapt to the changing times?—will find much of interest and value between these covers. The reader will quickly discover about the author—what the well-informed American internist already knows—that his keenly observing, sensitive nature has been fostered by an excellent medical education—both before and after graduation—and leavened by his years of practice in New York City. Pleasant glimpses of his love of the sea and of music and the arts are frequent. Incidentally, the rather hard, calculating physiognomy portrayed on the jacket is, to the Reviewer at least, an unfortunate libel on Dr. Binger's sensitive, intellectual, yes, handsome features. In 18 more or less connected chapters, the author interprets the changes that have come over medicine—the expansion of medical science; the disappearance of "the encyclopedic wise man" ("It is only a few years since doctors came out from behind the ambush of their beards"); growth of the specialties; the socialization of medicine; psychoanalysis and psychosomatic medicine (an irritating word for something that the real doc has always practiced!); and some of the popular diseases of our time. Much is being written on these matters—tripe and otherwise—but one must go far to find more penetrating, wiser comments than appear throughout this book. To be sure, "I" might appear less often in the text to advantage; racial discrimination looms over-prominently; the belief that the general practitioner is on the way out will be denied by many; and the author has fallen into the frequent error of intimating that reform in medical education in the U. S. really owes all to the founding of Johns Hopkins and to Abraham Flexner's report. But these are minor criticisms that are soon effaced by the torrent of fundamental wisdom, set off by apt quotations from Paracelsus and others and by the author's own trenchant observations: "the secret of the care of the patient is in caring for the patient" (F. W. P.);

"he who wants to know man must look upon him as a whole" (P. A. T. B. von H.); the internist is "the conductor of the symphony who calls out the oboe and the tympanum and does not let either steal the show" (C. B.); as to the need for choosing a good doctor "a *pretty* good doctor is like a *pretty* good egg" (George Sears); "the patient should be in more or less continuous contact with a doctor whom he knows and trusts . . . and stick to him and take his advice until he is done with him and then choose another. . . . It is far more important that he possess integrity" (than brilliance) (C. B.); "When a clinic record reaches a certain thickness, a certain weight, the patient is usually referred for a psychiatric consultation" (H. B. R. in *Patients Have Families*); "We must have more doctors trained in both medicine and psychiatry. . . . There is almost no department of human behavior that does not fall into the province of the psychiatrist's interest" (C. B.); "Like happiness a cure is seldom found by searching for it" (C. B.). In a final paragraph we find among the obstacles to the good physician's task: "Our patients demand miracles of us. They limit our moves by making pawns of us—or kings—when we should range freely as knights. . . . These (our professional standards) we fight for gladly. It is indeed a poor heart that never rejoices."

E. K.

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### NEW BOOKS

*The Medical Clinics of North America.* Symposium on New Developments in Medicine. Pp. 561; 96 figs. Phila.: Saunders, 1945. \$16 per year.

*On Modern Syphilotherapy.* With Particular Reference to Salvarsan. By ALBERT NEISSER. Translated by ISABELLE VON SAZENHOFEN WARTENBERG. Pp. 42. Baltimore: Johns Hopkins Press, 1945. Price, \$1.00.

*Proceedings of the Rudolf Virchow Medical Society in the City of New York.* Pp. 103. Vol. III, 1944. New York: Brooklyn Medical Press, 1945. Price, \$2.00.

*Mass Radiography of the Chest.* By HERMAN E. HILLEBOE, M.D., Medical Director, Chief, Tuberculosis Control Division, United States Public Health Service; Professorial Lecturer on Tuberculosis Control, George Washington Univ. School of Medicine, Washington, D. C., and RUSSELL H. MORGAN, M.D., Surgeon (R), Medical Officer-in-Charge, Radiology Section, Tuberculosis Control Division, United States Public Health Service. Pp. 288; 93 figs. Chicago: Year Book Publishers, 1945. Price, \$3.50.

*Malaria in the Upper Mississippi Valley (1760-1900)* (Supplements to the Bulletin of the History of Medicine). By ERWIN H. ACKERKNECHT. Pp. 142. Baltimore: Johns Hopkins Press, 1945. Price, \$2.00 (\$1.75 to subscribers).

*A Manual of Tropical Medicine.* Prepared under the Auspices of the Division of Medical Sciences of the National Research Council. By COL. THOMAS T. MACKIE, M.C., A.U.S. (and 8 others). Pp. 727; 287 ills., 6 in color. Phila.: Saunders, 1945.

*BRONCHIAL ASTHMA.* By LEON UNGER, B.S., M.D., F.A.C.P., Assistant Professor, Department of Medicine, Northwestern Univ. Medical School, Chicago. Introduction by MORRIS FISHBEIN, M.D., Editor, *Journal of the American Medical Association*. Pp. 724; 117 ills. Baltimore: Thomas, 1945. Price, \$9.00.

*The New York Hospital. A History of the Psychiatric Service (1771-1936).* By WILLIAM LOGIE RUSSELL, Professor of Psychiatry, Emeritus, Cornell Univ. Med. Coll., Consulting Psychiatrist, New York Hosp. Pp. 556. New York: Columbia Univ. Press, 1945. Price, \$7.50.

*Doctors at War.* Edited by MORRIS FISHBEIN, M.D., Editor of the *Journal of the American Medical Association* and of *Hygeia*, The Health Magazine; Chief Editor of *War Medicine*; and Chairman of the Committee on Information of the Division of Medical Sciences of the National Research Council. Pp. 398; 82 photos, plus charts and diagrams and an index. New York: Dutton, 1945. Price, \$5.00.

*The Examination of Reflexes.* By ROBERT WARTENBERG, M.D. Foreword by FOSTER KENNEDY, M.D. Pp. 222. Chicago: Year Book Publishers, 1945. Price, \$2.50.

*Dietotherapy.* Clinical Application of Modern Nutrition. Edited by MICHAEL G. WOHL, M.D., Associate Professor of Medicine, Temple Univ., School of Medicine; Chairman, Advisory Committee on Nutrition, Philadelphia Department of Public Health. With a Foreword by RUSSELL M. WILDER, M.D., Ph.D., Professor of Medicine and Chief of the Department of Medicine, Mayo Foundation. Pp. 1029; 90 figs. Phila.: Saunders, 1945.

### NEW EDITIONS

*Technique of the Standard Kahn Test and of Special Kahn Procedures.* By REUBEN L. KAHN, Chief of Clinical Laboratories, Univ. of Michigan Hosp. Pp. 52. Revised and Enlarged Edition. Michigan: University of Michigan, 1944. Price, \$25.

*The Human Body.* By LOGAN CLENDENING, M.D. 4th Ed., corrected, enlarged, and rewritten. Pp. 443; over 100 ills. New York: Knopf, 1945. Price, \$4.00.

*The New-born Infant.* A Manual of Obstetrical Pediatrics. By EMERSON L. STONE, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale Univ.; Attending Obstetrician and Gynecologist to the New Haven Hosp. 3rd Ed., thoroughly revised. Pp. 314. Phila.: Lea & Febiger, 1945. Price, \$3.25.

*The Fundamentals of Electrocardiographic Interpretation.* By J. BAILEY CARTER, M.D., F.A.C.P., Assistant (Rush) Professor, Department of Medicine, Univ. of Illinois Coll. of Medicine; Attending Staff, Cook County Hosp., Augustana Hosp., Chicago. 2nd Ed. Pp. 406, 307 figs. Springfield: Thomas, 1945. Price, \$6.00.

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# INDEX

## A

- Abdominal crises in uncomplicated sickle cell anemia, 722
- Aberrant atrio-ventricular conduction in a case showing a short P-R interval and an abnormal but not prolonged QRS complex, 199
- Acetate and acetoacetate oxidation with  $C^{13}$ , A study of the intermediates of, 549
- Acetylcholine at phase boundary between cholesterol and saline, Electrical activity of, 267
- Acromegaly, Joint disease associated with, 671
- Aerosol suspension as indicated by pulmonary tuberculosis in rabbits, The behavior of inhaled particles in different states of, 412
- Agglutinins to the course of primary atypical pneumonia, The relationship of cold, 48
- Air sterilization, The present status of glycol vapors in, 162
- Air-borne infection by the disinfection of air, Measurement of, 177
- Scarlet fever as an, 64
- infections, Symposium, 55, 58, 64, 69, 74, 75
- tuberculosis, Experimental, 156
- Allergic disease, unexplained fatigue and lymphadenopathy; possible diagnostic confusion with infectious mononucleosis, The coincidence of, 306
- Anaerobic septicemia. Report of 6 cases with clinical bacteriologic and pathologic studies, 296
- Anderson, J. E., *see* Faegre, M. L., 557
- Anderson, T. F., Chemical structures of co-factors for bacterial viruses, 694
- Anemia and carcinoma of the stomach—autopsy studies concerning their interrelationship, Pernicious, 339
- in 3000 Canal Zone examinations upon natives of Central America, The incidence of sickle cell and sickle cell, 181
- Anthony, E., *see* Griffith, J. Q., 815
- Anticonvulsant effects of steroids, 548
- Antigens in saline-in-oil emulsion, Reduced acute toxicity of, 411
- Antistaphylococcal activity of various sulfonamides, The. With a method for routine determination of chemotherapeutic activity, 621
- Arthritis, Developments in, 364
- Ascorbic acid, The mechanism of the virucidal action of, 693
- Asthma, Penicillin in the treatment of intractable bronchial, 784
- Atabrine, Hematological changes produced by large doses of, 411
- Atrio-ventricular conduction in a case showing a short P-R interval and an abnormal but not prolonged QRS complex, Aberrant, 199
- Aycock, W. Lloyd, Lutman, Grace E., and Foley, George E., Seasonal prevalence as a principle in epidemiology, 395

## B

- Barnes, Mildred W., *see* Finland, 455
- Barnes, T. Cunliffe, *see* Beutner, R., 267
- Bauer, Walter, *see* Waine, Hans, 671
- Beerman, Herman, Biologic false positive reactions to the tests for syphilis, 525
- Bennett, G. A., *see* Waine, Hans, 671
- Bertucci, E., Leptospirosis, 86
- Beutner, R., and Barnes, T. Cunliffe, Electrical activity of acetylcholine at phase boundary between cholesterol and saline, 267
- Beyer, K. H., Verwey, W. F., Woodward, R., Peters, L., and Mattis, P. A., The enhancement of the plasma concentration of penicillin in dogs by the simultaneous administration of para-aminohippuric acid, III, 608
- Bismuth sodium tartrate, The treatment of tularemia with intravenous, 513
- Blain, A., and Vonder Heide, E. C., Infectious mononucleosis and the Negro. With a report of 6 cases, 587
- Blake, Alton D., *see* Strumia, Max M., 436
- Block, Coronary insufficiency, revealed by ectopic nodal and ventricular beats in the presence of left bundle branch, 349
- Blood levels of sulfonamides, Factors influencing the maintenance of, 813
- procurement project, Complications arising in donors in a mass, 421
- Bone marrow extracts, Recent studies on yellow, 717
- Bowie, M., *see* Richardson, R., 1
- Boynton, Mary Heiss, and Taylor, Major Earl S., Complications arising in donors in a mass blood procurement project, 421
- Brieger, H., Carbon monoxide polycythemia, 129
- Bromsalizol in lengthening the effect of a sympathetic nerve block, The use of, 314
- Bronchial distribution, Subdivision of the lung on the basis of, 550



- Brown, J. Howard, and Schaub, Isabelle G., The relation of streptococci to human disease: Importance of identification and nomenclature. II. Streptococci other than those of Group A, 388
- Brucella abortus *in vivo*, Inadequate action of, Penatin against, 78
- Buchanan, J. M., Sakami, W., Gurin, S., and Wilson, D. Wright, 549
- Bullitt, I., *see* Koop, E., 28
- Burch, G. E., A method for measuring small amounts of weight loss in man, 220
- Burch, G. E., and Winsor, T., The relation of total insensible loss of weight to water loss from the skin and lungs of human subjects in a subtropical climate, 226
- Burns, Changes in the non-protein fractions of the plasma nitrogen following extensive thermal, 413
- Burrett, John B., and White, Paul D., Large interauricular septal defect with particular reference to diagnosis and longevity. Report of 2 new cases, 355
- C**
- C<sup>13</sup>, A study of the intermediates of acetate and acetoacetate oxidation with, 549
- Caldwell, J. E., Sifferd, R. H., Porsche, J. D., and Fenger, F., Recent studies on yellow bone marrow extracts, 717
- Canal Zone examinations upon natives of Central America, The incidence of sickle cell anemia and sickle cell anemia in 3000, 181
- Carbon monoxide polycythemia, 129
- Cardiac examination of 23,000 inductees and volunteers, Initial, 657
- hypertrophy and extramedullary erythropoiesis in newborn infants of prediabetic mothers, 447
- studies, 2. Diabetes mellitus, etc., 8
- Cerebral coccidioidomycosis with cultural studies, A fatal case of, 483
- Cheever, F., The control of meningococcal meningitis by mass chemoprophylaxis with sulfadiazine, 74
- Chemoprophylaxis with sulfadiazine, The control of meningococcal meningitis by mass, 74
- Chemotherapeutic activity, With a method for routine determination of. The antistaphylococcal activity of various sulfonamides, 621
- properties of streptomycin, 128
- Chenoweth, B., *see* Hodes, H., 64
- Chest, Clinical aspects of pain in the. II. Pain arising from the esophagus, 765
- III. Pain arising from the stomach, 771
- Chickenpox as air-borne diseases, Mumps and, 75
- Childhood, The intra-duodenal secretions in, 788
- Chornock, F. W., *see* Strumia, Max M., 436
- Chouke, K., Repair following tucking operations on the extra-ocular muscles, 127
- Circulation, The effect of respiratory movements upon the, 814
- Clark, Elizabeth A., *see* Pohle, Ernst A., 503
- Clark, Guy W., Vitamin content of liver extracts for parenteral use. A comparison of crude and concentrated preparations, 520
- Clark, I., *see* Silber, R. H., 804
- Clotting time of the recalcified plasma, With a note on the. Hemophilia-like disease in the female, 443
- Coccidioidomycosis with cultural studies, A fatal case of cerebral, 483
- Co-factors for bacterial viruses, Chemical structures of, 694
- Commission on acute respiratory diseases, 1. Atypical pneumonia, 55
- Comroe, B. I., Failure of penicillin in rheumatoid arthritis, 646
- Comroe, J. H., Dripps, R. D., Dumke, P. R., and Deming, M., Effects produced in man by inhalation of high concentration of oxygen for 24 hours, 814
- Cooke, R. A., *see* Leopold, S. S., 784
- Cooley, T. B., A severe type of hereditary anemia with elliptocytosis. Interesting sequence of splenectomy, 561
- Corcoran, A. C., *see* Page, I. H., 557
- Coronary insufficiency, revealed by ectopic nodal and ventricular beats in the presence of left bundle branch block, 349
- Cystadenoma of the ovary, Meigs' syndrome in a case of multilocular pseudomucinous, 327
- D**
- Davis, O. T., Harrell, G. T., and King, E. S., The effect of simultaneous tuberculous infection on experimental trichinella infestations in guinea pigs, 658
- de Forest, G. K., and Kerr, L. M., A case of eczema as a source of a streptococcal epidemic, 752
- Deming, Margo, *see* Comroe, J. H., 814
- de Renyi, George S., The nature of intercalated disks of cardiac muscle studied by the microdissection method, 270
- (Diabetes) Cardiac hypertrophy and extramedullary erythropoiesis in newborn infants of prediabetic mothers, 447
- Diabetes mellitus as observed in 100 cases for 10 or more years:
1. General observations, 1
  2. Cardiac studies, 8
  3. Ocular findings, 16
  4. Peripheral vascular findings in 89 of these cases, 23

- Diefendorf, H. W., *see* Kent, G. T., 640  
 Diethylstilbestrol with report of a case, The hepatotoxic action of, 602  
 Diet, Studies on the prolonged maintenance of adult dogs on a purified, 692  
 Digilanid and the therapy of congestive heart disease, 33  
 Disinfection of air, Measurement of air-borne infection by the, 177  
 Donors in a mass blood procurement project, Complications arising in, 421  
 Drabkin, David L., Crystallographic and optical properties of human hemoglobin. A proposal for the standardization of hemoglobin, 268  
 Dripps, R. D., *see* Comroe, J. H., 814  
 Du Buy, H. G., and Hollaender, A., Sampling devices, 172  
 Dumke, P. R., *see* Comroe, J. H., 814  
 Duodenal secretions in childhood, The intra-, 788  
 Dust-borne bacteria, Recent studies on the control of, 166

## E

- Ectopic nodal and ventricular beats in the presence of left bundle branch block, Coronary insufficiency, revealed by, 349  
 Eczema as a source of a streptococcal epidemic, A case of, 752  
 Edeiken, J., Diabetes mellitus, etc. 2. Cardiac studies, 8  
 Ehrich, W., Harris, T., Observations on the function of the lymphocyte, 129  
 Electroencephalographic changes during the scotomas of migraine, Focal, 650  
 Elias, H., and Schwimmer, D., The hepatotoxic action of diethylstilbestrol with report of a case, 602  
 Elliptocytosis, A severe type of hereditary anemia with. Interesting sequence of splenectomy, 561  
 Engel, G. L., Ferris, E. B., and Romano, J., Focal electroencephalographic changes during the scotomas of migraine, 650  
 Englehorn, T. D., and Wellman, W. E., Filariasis in soldiers on an island in the South Pacific, 141  
 Enzer, Norbert, *see* Simonson, Ernst, 349  
 Enzymological investigations on experimental tuberculosis in rabbits, 548  
 Eosinophilia following parenteral liver therapy. Literature and case report, 572  
 Eosinophils in thrombocytopenic purpura, The prognostic value of marrow, 579  
 Epidemiology, Seasonal prevalence as a principle in, 395  
 Equilibria between the erythrocyte and a complex external solution, Osmotic and ionic, 413

- Ercoli, B., Lewis, M. N., and Harker, Eleanor M., The antistaphylococcal activity of various sulfonamides. With a method for routine determination of chemotherapeutic activity, 621  
 Erythrocyte and a complex external solution, Osmotic and ionic equilibria between the, 413  
 Erythrocytes as a plasma substitute, The use of a "modified globin" from human. Preliminary report, 436  
 Erythropoiesis in newborn infants of prediabetic mothers, Cardiac hypertrophy and extramedullary, 447  
 Esophagus, II. Pain arising from the. Clinical aspects of pain in the chest, 765  
 Experimental gastric ulcer in the rat, A method for the uniform production of, 549  
 Extra-ocular muscles, Repair following tucking operations of the, 127

## F

- Fabricant, Noah D., The tonsil-adenoid problem, 542  
 Fatigue, unexplained, and lymphadenopathy; possible diagnostic confusion with infectious mononucleosis, The coincidence of allergic disease, 306  
 Fenger, F., *see* Caldwell, J. E., 717  
 Ferris, E. B., *see* Engel, G. L., 650  
 Filariasis in soldiers on an island in the South Pacific, 141  
 Finland, M., *see* Goodwin, R. A., 628  
 Finland, Maxwell, Parker, Frederic, Barnes, Mildred W., and Joliffe, Capt. Leslie S., Acute myocarditis in influenza infections. Two cases of non-bacterial myocarditis, with isolation of virus from the lungs, 455  
 Flaxman, Nathan, Initial cardiac examination of 23,000 inductees and volunteers, 657  
 Florsdorf, E. W., and Mudd, Stuart, Drying penicillin, 894  
 Foley, George E., *see* Aycock, W. Lloyd, 395  
 Fox, Max J., and Sennett, Louis, Polio-myelitis in pregnancy, 382  
 Fox, T. T., Aberrant atrio-ventricular conduction in a case showing a short P-R interval and an abnormal but not prolonged QRS complex, 199  
 Friedland, C. K., *see* Starr, Isaac, 814

## G

- Gastric ulcer in the rat, A method for the uniform production of experimental, 549  
 Gelatin as a plasma substitute. The effect of gelatin infusion of the subsequent typing and cross-matching of the blood, with a method of eliminating the phenomenon of pseudoagglutination, 28

- Giffin, H. Z., *see* Hall, B. E., 712  
 Glomerulonephritis, Retinopathy in, 257  
 Glycol vapors in air sterilization, The present status of, 162  
 Goodman, Jay S., *see* Simonson, Ernst, 349  
 Goodwin, R. A., Wilcox, C., and Finland, M., Persistence of pneumococci in sulfonamide treated cases of pneumonia, 628  
 Graessle, O., *see* Robinson, H., 128  
 Griffith, J. Q., Padis, N., and Anthony, E., Treatment of clinical hyper-pituitarism with hypertension by injections of pitressin tannate in oil, 815  
 Gruenstein, M., *see* Shay, H., 549  
 Gubner, Richard, Szucs, Murrill, and Ungerleider, Harry E., Provocative prolongation of the P-R interval in rheumatic fever, 469  
 Gunther, L., *see* Henstell, H. H., 187  
 Gurin, S., *see* Buchanan, J. M., 549

## H

- Habel, K., Mumps and chickenpox as air-borne diseases, 75  
 Hall, B. E., Watkins, C. H., and Giffin, H. Z., Radioactive phosphorus in the treatment of polycythemia vera, 712  
 Halbert, S. P., Smolens, J., and Mudd, S., Reduced acute toxicity of antigens in saline-in-oil emulsion, 411  
 Hamburger, M., Jr., Robertson, O. H., Puck, T. T., The present status of glycol vapors in air sterilization, 162  
 Hanno, H. A., and Mensh, M., Eosinophilia following parenteral liver therapy. Literature and case report, 572  
 Hargraves, M. M., *see* Hall, B. E., 712  
 Harker, E. M., *see* Ercoli, M. N., 621  
 Harrell, G. T., *see* Davis, O. T., 758  
 Harris, T., *see* Ehrich, W., 129  
 Harris, T. N., and Stokes, J., Jr., Summary of a 3-year study of the clinical applications of the disinfection of air by glycol vapors, 152  
 Harrison, T. R., Clinical aspects of pain in the chest. II. Pain arising from the esophagus, 765  
     III. Pain arising from the stomach, 771  
 Hayman, Lt. Col. Joseph, Jr., and Read, Major William A., Some clinical observations on an outbreak of jaundice following yellow fever vaccination, 281  
 Heart disease, Digilanid and the therapy of congestive, 33  
 (Hematocrit) volumes and lymphocyte counts, A relation between cell-pack, 336  
 Hematological changes produced by large doses of atabrine, 411  
 Hemoglobin, Crystallographic and optical properties of human. A proposal for the standardization of hemoglobin, 268

- Hemophilia-like disease in the female. With a note on the clotting time of the recalcified plasma, 443  
 Henstell, H. H., and Gunther, L., Studies of plasma volume in the human being. Comparative results of reduction of plasma volume, intramuscular pressure and venous pressure in surgical shock, 187  
 Hepatotoxic action of diethylstilbestrol with report of a case, The, 602  
 Hepler, Opal E., *see* Jung, Frederic T., 336  
 Hereditary anemia with elliptocytosis, A severe type of. Interesting sequence of splenectomy, 561  
 Hess, C. B., The Rh factor in pregnancy, 804  
 Hettig, Robert A., *see* Randolph, Theron G., 306  
 Heyman, Albert, Acute syphilitic meningitis. A discussion of the problems encountered in the diagnosis, 664  
 Hodes, H., Schwentker, F., Chenoweth, B., and Peck, J., Scarlet fever as an air-borne infection, 64  
 Hollaender, A., *see* Du Buy, H. G., 172  
 Howe, John S., *see* Reid, J. Douglas, 296  
 Huber, J. F., Subdivision of the lung on the basis of bronchial distribution, 550  
 Hyper-pituitarism with hypertension by injections of pitressin tannate in oil, Treatment of clinical, 815  
 Hypertension by injections of pitressin tannate in oil, Treatment of clinical hyper-pituitarism with, 815

## I

- Inductees and volunteers, Initial cardiac examination of 23,000, 657  
 Infectious mononucleosis, The coincidence of allergic disease, unexplained fatigue, and lymphadenopathy; possible diagnostic confusion with, 306  
 Infiltration, Diagnostic and therapeutic aspects of local. Somatic pain, 240  
 Influenza infections. Two cases of non-bacterial myocarditis, with isolation of virus from the lungs, Acute myocarditis in, 455  
 Interauricular septal defect with particular reference to diagnosis and longevity, Large. Report of 2 new cases, 355  
 Intercalated disks of cardiac muscle studied by the microdissection method, The nature of, 270

## J

- Jacobs, M. H., and Stewart, D. R., Osmotic and ionic equilibria between the erythrocyte and a complex external solution, 413

- Jackson, Will W., The treatment of tularemia with intravenous bismuth sodium tartrate, 513  
 Jaundice following yellow fever vaccination, Some clinical observations on an outbreak of, 281  
 Johnston, C. G., Refrigeration in surgery, 253  
 Joint disease associated with acromegaly, 671  
 Joliffe, Capt. L. S., *see* Finland, Maxwell, 455  
 Jones, T., *see* Wheeler, S., 58  
 Judovich, B., Somatic pain. Diagnostic and therapeutic aspects of local infiltration, 240  
 Jung, Frederic T., Hepler, Ópal E., and Maynard, Mason S., A relation between cell-pack (hematocrit) volumes and lymphocyte counts, 336

## K

- Kaplan, Henry S., and Rigler, Leo G., Pernicious anemia and carcinoma of the stomach—autopsy studies concerning their interrelationship, 339  
 Karr, Walter G., *see* Strumia, Max M., 436  
 Kent, G. T., and Diefendorf, H. W., A clinical study of sensitivity to sulfathiazole, 640  
 Kerr, L. M., *see* de Forest, G. K., 752  
 King, E. S., *see* Davis, O. T., 758  
 Klein, Morton, The mechanism of the virucidal action of ascorbic acid, 693  
 Kocholaty, W., *see* Stubbs, E., 78  
 Kolm, R., Komarov, S., and Shay, H., Experimental studies on the excretion of neutral red by the stomach, 693  
 Komarov, S., *see* Kolm, R., 693  
 Komarov, S. A., *see* Shay, H., 549  
 Koop, E., and Bullitt, L., Gelatin as a plasma substitute. The effect of gelatin infusion on the subsequent typing and cross-matching of the blood, with a method of eliminating the phenomenon of pseudoagglutination, 28

## L

- Lee, Ferdinand C., Macht, David, I., and Pierpont, Ross Z., The use of bromsalizol in lengthening the effect of a sympathetic nerve block, 314  
 Leopold, I., Diabetes mellitus, etc. 3. Ocular findings, 16  
 Leopold, S. S., and Cook, R. A., Penicillin in the treatment of intractable bronchial asthma, 784  
 Leptospirosis, 86  
 Lewis, M. N., *see* Ercoli, B., 621  
 Live, I., *see* Stubbs, E., 78  
 Liver extracts for parenteral use, Vitamin content of. A comparison of crude and concentrated preparations, 520

- Liver therapy, Eosinophilia following parenteral. Literature and case report, 572  
 Loosli, C. G., and Robertson, O. H., Recent studies on the control of dust-borne bacteria by treatment of floors and bedclothes with oil, 166  
 Lubin, A., Relationship and function of the pyramidal tract, 111  
 Luisada, A. A., and Wolff, L., The significance of the pulmonary diastolic murmur in cases of mitral stenosis, 204  
 Lung on the basis of bronchial distribution, Subdivision of the, 550  
 Lurie, M. B., Experimental air-borne tuberculosis, 156  
 Lutman, Grace E., *see* Aycock, W. Lloyd, 395  
 Lymphadenopathy, The coincidence of allergic disease, unexplained fatigue, and; possible diagnostic confusion with infectious mononucleosis, 306  
 Lymphocyte counts, A relation between cell-pack (hematocrit) volumes and, 336  
 lymphocyte, Observations on the function of the, 129

## M

- Macht, David I., *see* Lee, Ferdinand C., 314  
 Madison, Frederick W., and Quick, Armand J., Hemophilia-like disease in the female. With a note on the clotting time of the recalcified plasma, 443  
 Masson, G., Spermatogenic activity of various steroids, 324  
 Mattis, P. A., *see* Beyer, K. H., 608  
 Maynard, Mason S., *see* Jung, Frederic T., 336  
 McConnell, J., An epidemic of pleurodynia with prominent neurologic symptoms and no demonstrable cause, 41  
 McNeil, C., The relationship of cold agglutinins to the course of primary atypical pneumonia, 48  
 Mediastinal emphysema with pneumothorax simulating organic heart disease, Spontaneous, 211  
 Meigs' syndrome in a case of multilocular pseudomucinous cystadenoma of the ovary, 327  
 Meningitis, Acute syphilitic. A discussion of the problems encountered in the diagnosis, 664  
 Meningococcal infections, The transmission and control of, 69  
 meningitis by mass chemoprophylaxis with sulfadiazine, The control of, 74  
 Mensh, M., *see* Hanno, H. A., 572  
 Meranze, D., *see* Shay, H., 549  
 Metabolism of the rat, The importance of insensible water loss in the, 268  
 Microdissection method, The nature of intercalated disks of cardiac muscle studied by the, 270

- Migraine, Focal electroencephalographic changes during the scotomas of, 650
- Miller, Herbert C., Cardiac hypertrophy and extramedullary erythropoiesis in newborn infants of prediabetic mothers, 447
- Miller, H., Spontaneous mediastinal emphysema with pneumothorax simulating organic heart disease, 211
- Millet, Joseph, and Shell, John, Meigs' syndrome in a case of multilocular pseudomucinous cystadenoma of the ovary, 327
- Mitral stenosis, The significance of the pulmonary diastolic murmur in cases of, 204
- Mononucleosis and the Negro, Infectious. With a report of 6 cases, 587
- Movitt, Capt. E. R., Spontaneous pneumothorax as a complication of pneumonia in adults, 595
- Mudd, S., *see* Halbert, S. P., 411
- Mudd, Stuart, *see* Flosdorf, 694
- Mumps and chickenpox as air-borne diseases, 75
- Mushett, Charles W., and Siegel, Henry, Hematological changes produced by large doses of atabrine, 411
- Myocarditis, with isolation of virus from the lungs, Acute myocarditis in influenza infections. Two cases of non-bacterial, 455
- N
- Naide, M., Diabetes mellitus, etc. 4. Peripheral vascular findings in 89 of these cases, 23
- Naide, Meyer, and Sayen, Ann, The primary influence of basal vascular tone on the development of postocclusive collateral circulation and in selecting patients for sympathectomy, 478
- Neel, J. V., and Valentine, W. N., The frequency of thalassemia, 568
- Neel, J. V., *see* Valentine, W. N., 741
- Neutral red by the stomach, Experimental studies on the excretion of, 693
- Non-protein fractions of the plasma nitrogen following extensive thermal burns, 413
- O
- Ocular findings, 3. Diabetes mellitus, etc., 16
- Osmotic and ionic equilibria between the erythrocyte and a complex external solution, 413
- Ovary, Meigs' syndrome in a case of multilocular pseudomucinous cystadenoma of the, 327
- Oxidation with  $C^{13}$ , A study of the intermediates of acetate and acetoacetate, 549
- Oxygen for 24 hours, Effects produced in man by inhalation of high concentration of, 814
- P
- Padis, N., *see* Griffith, J. Q., 815
- Page, I. H., *see* Taylor, R. D., 235
- Para-aminohippuric acid, III, The enhancement of the plasma concentration of penicillin in dogs by the simultaneous administration of, 608
- Parker, Frederic, *see* Finland, Maxwell, 455
- Paul, Lester W., *see* Pohle, Ernst A., 503
- Peck, J., *see* Hodes, H., 64
- Peirce, J. D., *see* Taylor, R. D., 235
- Pemberton, Ralph, Developments in arthritis, 364
- Penatin against brucella abortus *in vivo*, Inadequate action of, 78
- Penicillin, drying, 694
- in dogs by the simultaneous administration of para-aminohippuric acid, III, The enhancement of the plasma concentration of, 608
- in rheumatoid arthritis, Failure of, 646
- in the treatment of intractable bronchial asthma, 784
- Peripheral vascular findings in 89 of these cases, 4. Diabetes mellitus, etc., 23
- Pernicious anemia and carcinoma of the stomach—autopsy studies concerning their interrelationship, 339
- Peters, L., *see* Beyer, K. H., 608
- Phair, J., and Schoenbach, E., The transmission and control of meningococcal infections, 69
- Phosphorus in the treatment of polycythemia vera, Radioactive, 712
- The therapeutic use of radioactive, 701
- Pierpont, Ross Z., *see* Lee, Ferdinand C., 314
- Pitressin tannate in oil, Treatment of clinical hyper-pituitarism with hypertension by injections of, 815
- Pituitary extract in tests of urinary concentration, Use of posterior, 235
- Plasma concentration of penicillin in dogs by the simultaneous administration of para-aminohippuric acid, III, 608
- Hemophilia-like disease in the female. With a note on the clotting time of the recalcified, 443
- nitrogen following extensive thermal burns, Changes in the non-protein fractions of the, 413
- substitute. The effect of gelatin infusion of the subsequent typing and cross-matching of the blood, with a method of eliminating the phenomenon of pseudoagglutination, Gelatin as a, 28
- The use of a "modified globin" from human erythrocytes as a. Preliminary report, 436

- Plasma volume in the human being, Studies of. Comparative results of reduction of plasma volume, intramuscular pressure and venous pressure in surgical shock, 187
- Pleurodynia with prominent neurologic symptoms and no demonstrable cause, An epidemic of, 41
- Pneumococci in sulfonamide treated cases of pneumonia, Persistence of, 628
- Pneumonia, Atypical, 55  
in adults, Spontaneous pneumothorax as a complication of, 595  
resembling primary atypical pneumonia, Pneumococci, 496  
The relationship of cold agglutinins to the course of primary atypical, 48
- Pneumothorax as a complication of pneumonia in adults, Spontaneous, 595  
simulating organic heart disease, Spontaneous mediastinal emphysema with, 211
- Pohle, Ernst A., Paul, Lester W., and Clark, Elizabeth, Roentgen therapy of Boeck's sarcoid, 503
- Polycythemia, Carbon monoxide, 129
- Polycythemia vera, Radioactive phosphorus in the treatment of, 712
- Poliomyelitis in pregnancy, 382
- Porsche, J. D., *see* Caldwell, J. E., 717
- Postocclusive collateral circulation and in selecting patients for sympathectomy, The primary influence of basal vascular tone on the development of, 478
- Pregnancy, Poliomyelitis in, 382  
The Rh factor in, 804
- P-R interval in rheumatic fever, Provocative prolongation of the, 469
- Pseudoagglutination, Gelatin as a plasma substitute. The effect of gelatin infusion of the subsequent typing and cross-matching of the blood, with a method of eliminating the phenomenon of, 28
- Puck, O. H., *see* Hamburger, M., 162
- Pulmonary diastolic murmur in cases of mitral stenosis, The significance of the, 204
- Pyramidal tract, Relationship and function of the, 111
- Q**
- Quick, Armand J., *see* Madison, Frederick W., 443
- R**
- Rabbits, Enzymological investigations on experimental tuberculosis in, 548
- Racker, E., Rose, S. P., and Tumen, A. O., Pneumococci pneumonia resembling primary atypical pneumonia, 496
- Radioactive phosphorus in the treatment of polycythemia vera, 712  
The therapeutic use of, 701
- Randolph, Theron G., and Hettig, Robert A., The coincidence of allergic disease unexplained fatigue and lymphadenopathy; possible diagnostic confusion with infectious mononucleosis, 306
- Ratcliffe, H. L., *see* Wells, W. F., 412
- Read, Major William A., M.C., *see* Hayman J., Lt. Col., 281
- Refrigeration in surgery, 253
- Reid, J. Douglas, Snider, George E., Toone, Elam C., and Howe, John S., Anaerobic septicemia. Report of 6 cases with clinical bacteriologic and pathologic studies, 296
- Respiratory infections with reference to streptococcal illness and acute rheumatic fever, Factors in the control of the spread of acute, 58  
movements upon the circulation, The effect of, 814
- Retinopathy in glomerulonephritis, 257
- Reviews (Reviewer's initials in parentheses):  
Abrahamsen, D., Crime and the Human Mind (N. Y.), 276  
Anson, M. L., and Edsall, J. T., Advances in Protein Chemistry, Vol. I (H. V.), 418  
Arnold, H., Poisonous Plants of Hawaii (E. K.), 132  
Bauer, Julius, Constitution and Disease (E. K.), 820  
Bauer, W. W., Contagious Diseases (V. C.), 556  
Bellows, J., Cataract and Anomalies of the lens (F. A.), 134  
Binger, Carl, The Doctor's Job (E. K.), 821  
Bispham, W. N., Malaria: Its Diagnosis, Treatment and Prophylaxis (H. R.), 557  
Blackfan, K. D., Atlas of the Blood in Children (E. K.), 275  
Boyd, William, The Pathology of Internal Diseases (W. S.), 819  
Bradstreet, R. B., The Standardization of Volumetric Solutions (W. S.), 273  
Brailsford, J. F., The Radiology of Bones and Joints (E. P.), 274  
Braun-Menendez, E., Hipertension Arterial Nefrogena (W. J.), 131  
Bundesen, H., The Baby Manual (I. W.), 131  
Cameron, A. T., Recent Advances in Endocrinology (E. K.), 556  
Cantarow, A., Lead Poisoning (N. A.), 558  
Comroe, B. I., Arthritis and Allied Conditions (E. K.), 551  
Corner, C. W., Ourselves Unborn (I. W.), 553  
da Costa, J. C., The Trials and Triumphs of the Surgeons, and Other Literary Gems (E. K.), 555  
Donaldson, J. K., Surgical Disorders of the Chest (L. S.), 418  
Everett, H. S., Gynecological and Obstetrical Urology (L. La T.), 276  
Fabricant, Noah D., The Common Cold and How to Fight It (M. K.), 817  
Faegre, M. L., and Anderson, J. E., Child Care and Training (I. W.), 557  
Fieser, L. F., and Fieser, M., Organic Chemistry (S. G.), 551  
Fishbein, Morris, Medical Uses of Soap (H. B.), 416  
Gould, S. E., Trichinosis (H. R.), 696  
Hamblen, E. C., Endocrinology of Woman (I. Z.), 416  
Harley, David, Medico-legal blood group determination (W. S.), 696  
Harries, E. H. R., and Mitman, M., Clinical Practice in Infectious Diseases. For Students, Practitioners and Medical Officers (T. M.), 275

*Reviews* (Reviewer's initials in parentheses):

- Harrower-Erickson, M. R., and Steiner, M. E., *Large Scale Rorschach Techniques* (N. Y.), 277
- Henderson, D. K., *A Text Book of Psychiatry for Students and Practitioners* (C. R.), 818
- Hewer, C., *Recent Advances in Anesthesia and Analgesia (Including Oxygen Therapy)* (R. D.), 134
- Jaeger, E., *A Source-Book of Biological Names and Terms* (E. K.), 132
- Kerr, H., *Urinary Tract* (L. La T.), 135
- Koch, F. C., *Practical Methods in Biochemistry* (W. S.), 274
- Loeb, Leo, *The Biological Basis of Individuality* (D. C.), 818
- Lowinger, A., *The Methodology of Pierre Duhem* (C. C.), 272
- Lull, C. B., *Control of Pain in Childbirth* (D. M.), 277
- Lyle, Donald J., *Neuro-Ophthalmology* (F. A.), 818
- McDonough, Mary Lou (compiled by), *Poet Physicians* (E. K.), 697
- McQuarrie, Irvine, *The Experiments of Nature and Other Essays* (I. W.), 696
- Medical Clinics of North America, New York Number. Symposium on Psychosomatic Medicine (H. B.), 133
- Medical Clinics of North America, Phila. No., Nov., 1944 (M. H.), 552
- Medical Clinics of North America. Symposium on Specific Methods of Treatment. The Boston Number (M. H.), 137
- Moore, R. A., *A Textbook of Pathology* (W. S.), 416
- Moseley, H. F., *Shoulder Lesions* (J. R.), 555
- Moulton, F. R., *Surface Chemistry* (W. S.), 273
- New York Academy of Medicine Lectures to the Laity, *The March of Medicine* (E. K.), 817
- Page, I. H., and Corcoran, A. C., *Arterial Hypertension* (J. G.), 557
- Portis, S., *Diseases of the Digestive System* (M. H.), 134
- Pratt, G. K., *Soldier to Civilian* (N. Y.), 552
- Richardson, H. B., *Patients Have Families* (G. R.), 697
- Sandell, E., *Colorimetric Determination of Traces of Metals* (D. D.), 137
- Sawyer, R., *Experimental Spectroscopy* (D. D.), 138
- Senn, M., *All About Feeding Children* (I. W.), 138
- Simmons, J., *Global Epidemiology* (D. P.), 133
- Smith, May, *Handbook of Industrial Psychology* (N. Y.), 553
- Smith, O., *Textbook of Rehabilitation* (A. R.), 132
- Strachey, A., *A New German-English Psycho-Analytical Vocabulary. Research Supplements to the International Journal of Psycho-Analysis* (J. M.), 275
- Stern, B. J., *American Medical Practice in the Perspectives of a Century* (G. R.), 554
- Templeton, F., *X-ray Examination of the Stomach* (E. P.), 136
- Thewlis, Malford W., *Metastases* (D. C.), 417
- Thimann, K. V., *Vitamins and Hormones* (H. V.), 418
- Wechsler, I. S., *The Neurologist's Point of View* (N. Y.), 820
- Whipple, D., and Aldrich, C., *Our American Babies* (I. W.), 137
- White, P. D., *Heart Disease* (E. K.), 419
- Wiggers, C. J., *Physiology in Health and Disease* (M. J.), 277
- Wilson, D. W., *A Laboratory Manual of Physiological Chemistry* (W. S.), 273

- Rheumatic fever, Factors in the control of the spread of acute respiratory infections with reference to streptococcal illness and acute, 58
- Provocative prolongation of the P-R interval in, 469
- Rheumatoid arthritis, Failure of penicillin in, 646
- Rh factor in pregnancy, The, 804
- Richardson, R., and Bowie, M., *Diabetes mellitus, etc., 1. General observations, 1*
- Rigler, Leo G., *see* Kaplan, Henry S., 339
- Rimmerman, A., *Digilanid and the therapy of congestive heart disease, 33*
- Robertson, O. H., *see* Hamburger, 162
- Robertson, O. H., *see* Loosli, C. G., 166
- Robinson, H., Graessle, O., and Smith, D., *Chemotherapeutic properties of streptomycin, 128*
- Roentgenologic problems, Notes on a variety of, 688
- Roentgen therapy of Boeck's sarcoid, 503
- Romano, J., *see* Engel, G. L., 650
- Rose, S. P., *see* Racker, E., 496

**S**

- Sakami, W., *see* Buchanan, J. M., 549
- Sampling devices, 172
- Sarcoid, Roentgen therapy of Boeck's, 503
- Sayen, Ann, *see* Naide, Meyer, 478
- Sarlet fever as an air-borne infection, 64
- Schaub, Isabelle G., *see* Brown, J. SchHoward, 388
- Schlumberger, Capt. Hans G., *A fatal case of cerebral coccidioidomycosis with cultural studies, 483*
- Schoenbach, E., *see* Phair, J., 69
- Schwartz, S. O., *The prognostic value of marrow eosinophils in thrombocytopenic purpura, 579*
- Schwentker, F., *see* Hodes, H., 64
- Schwimmer, D., *see* Elias, H., 602
- Scotomas of migraine, Focal electroencephalographic changes during the, 650
- Seasonal prevalence as a principle in epidemiology, 395
- Seeler, A. O., and Silber, R. H., *Studies on the prolonged maintenance of adult dogs on a purified diet, 692*
- Septal defect with particular reference to diagnosis and longevity, Large interauricular. Report of 2 new cases, 355
- Septicemia, Anaerobic. Report of 6 cases with clinical, bacteriologic and pathologic studies, 296
- Shay, H., Komrov, S. A., Gruenstein, M., Siplet, H., and Meranze, D., *A method for the uniform production of experimental gastric ulcer in the rat, 549*
- Shay, H., *see* Kolm, R., 693
- Shell, John, *see* Millett, Joseph, 327

- Sickle cell anemia, Abdominal crises in uncomplicated, 722
- Sickle cell anemia and sickle cell anemia in 3000 Canal Zone examinations upon natives of Central America, The incidence of, 181
- Siegel, H., *see* Mushett, C. W., 411
- Sifferd, R. H., *see* Caldwell, J. E., 717
- Silber, R. H., and Clark, I., Factors influencing the maintenance of blood levels of sulfonamides, 813
- Silber, R. H., *see* Seeler, A. O., 692
- Simonson, Ernst, Enzer, Norbert, and Goodman, Jay S., Coronary insufficiency, revealed by ectopic nodal and ventricular beats in the presence of left bundle branch block, 349
- Siplet, H., *see* Shay, H., 549
- Smith, D., *see* Robinson, H., 128
- Smolens, J., *see* Halbert, S. P., 411
- Snider, George E., *see* Reid, J. Douglas, 296
- Soldiers on an island in the South Pacific, Filariasis in, 141
- Somatic pain. Diagnostic and therapeutic aspects of local infiltration, 240
- Sperling, F., *see* Stubbs, E., 78
- Spermatogenic activity of various steroids, 324
- Spiegel, E. A., and Wycis, H. T., Anticonvulsant effects of steroids, 548
- Splenectomy, Interesting sequence of. A severe type of hereditary anemia with elliptocytosis, 561
- Starr, Isaac, and Friedland, C. K., The effect of respiratory movements upon the circulation, 814
- Steroids, Anticonvulsant effects of, 548
- Spermatogenic activity of, 324
- Stewart, D. R., *see* Jacobs, M. H., 413
- Stokes, J., Jr., *see* Harris, T. N., 152
- Stomach—autopsy studies concerning their interrelationship, Pernicious anemia and carcinoma of the, 339
- Experimental studies on the excretion of neutral red by the, 693
- III. Pain arising from the. Clinical aspects of pain in the chest, 771
- Streptococcal epidemic, A case of eczema as a source of a, 752
- illness and acute rheumatic fever, Factors in the control of the spread of acute respiratory infections with reference to, 58
- Streptococci to human disease, The relation of: Importance of identification and nomenclature. II. Streptococci other than those of Group A, 388
- Streptomycin, Chemotherapeutic properties of, 128
- Strumia, Max M., The use of a "modified globin" from human erythrocytes as a plasma substitute. Preliminary report, 436
- Stubbs, E., Live I., Sperling, F., and Kocholaty, W., Inadequate action of penatin against *Brucella abortus in vivo*, 78
- Sulfathiazole, A clinical study of sensitivity to, 640
- Sulfonamide treated cases of pneumonia, Persistence of pneumococci in, 628
- Sulfonamides, Factors influencing the maintenance of blood levels of, 813
- The antistaphylococcal activity of various. With a method for routine determination of chemotherapeutic activity, 621
- Surgery, Refrigeration in, 253
- Surgical shock, comparative results of reduction of plasma volume, intramuscular pressure and venous pressure in. Studies of plasma volume in the human being, 187
- Sympathectomy, The primary influence of basal vascular tone on the development of postocclusive collateral circulation and in selecting patients for, 478
- Sympathetic nerve block, The use of bromsalizol in lengthening the effect of, 314
- Syphilis, Biologic false positive reactions to the tests for, 525
- Syphilitic meningitis, Acute. A discussion of the problems encountered in the diagnosis, 664
- Szucs, Murrill, *see* Gubner, Richard, 469

## T

- Target cells, The artificial production and significance of, 741
- Taylor, Major Earl S., *see* Boynton, Mary Heiss, 421
- Taylor, R. D., Peirce, J. D., and Page, I. H., Use of posterior pituitary extract in tests of urinary concentration, 235
- Tennent, David M., The importance of insensible water loss in the metabolism of the rat, 268
- Thalassemia, The frequency of, 568
- Therapeutic aspects of local infiltration, Diagnostic and, Somatic pain, 240
- use of radioactive phosphorus, The, 701
- Thrombocytopenic purpura, The prognostic value of marrow eosinophils in, 579
- Tomlinson, W. J., Abdominal crises in uncomplicated sickle cell anemia, 722
- Tomlinson, W. J., The incidence of sickle cell anemia and sickle cell anemia in 3000 Canal Zone examinations upon natives of Central America, 181
- Tonsil-adenoid problem, The, 542
- Toone, Elam C., *see* Reid, J. Douglas, 296
- Toxicity of antigens in saline-in-oil emulsion, Reduced acute, 411



- Trichinella* infestations in guinea pigs,  
The effect of simultaneous tuberculous  
infection on experimental, 758  
Tuberculosis, Experimental air-borne,  
156  
in rabbits, Enzymological investiga-  
tions on experiment, 548  
Tuberculous infection on experimental  
*trichinella* infestations in guinea pigs,  
The effect of simultaneous, 758  
Tularemia with intravenous bismuth  
sodium tartrate, The treatment of, 513  
Tumen, A. O., *see* Rucker, E., 496

## U

- Ungerleider, Harry E., *see* Gubner,  
Richard, 469  
Urinary concentration, Use of posterior  
pituitary extract in, 235

## V

- Vaccination, Some clinical observations  
on an outbreak of jaundice following  
yellow fever, 281  
Valentine, W. N., and Neel, J. V., The  
artificial production and significance of  
target cells, 741  
Valentine, W. N., *see* Neel, J. V., 568  
Vascular tone on the development of post-  
occlusive collateral circulation and in  
selecting patients for sympathectomy,  
The primary influence of basal, 478  
Verwey, W. F., *see* Beyer, K. H., 608  
Virucidal action of ascorbic acid, The  
mechanism of the, 693  
Viruses, Chemical structures of co-fac-  
tors for bacterial, 694  
Virus from the lungs, Two cases of non-  
bacterial myocarditis, with isolation of.  
Acute myocarditis in influenza infec-  
tions, 455  
Vitamin content of liver extracts for  
parenteral use. A comparison of crude  
and concentrated preparations, 520  
Vonder Heide, E. C., *see* Blain, A., 587

## W

- Wagener, H. P., Retinopathy in glomer-  
ulonephritis, 257  
Waine, Hans, Bennet, G. A., and Bauer,  
W., Joint disease associated with  
acromegaly, 671  
Walker, James, Jr., Changes in the non-  
protein fractions of the plasma nitro-  
gen following extensive thermal burns,  
413  
Warren, Shields, The therapeutic use of  
radioactive phosphorus, 701  
Water loss in the metabolism of the rat,  
The importance of insensible, 268  
Watkins, C. H., *see* Hall, B. E., 712  
Weber, H. M., Notes on a variety of  
roentgenologic problems, 688  
Weight loss in man, A method for meas-  
uring small amounts of, 220  
to water loss from the skin and lungs  
of human subjects in a subtropical  
climate, The relation of total in-  
sensible loss of, 226  
Weiss, C., and Halliday, N., Enzymo-  
logical investigations on experiment  
tuberculosis in rabbits, 548  
Wellman, W. E., *see* Englehorn, T. D.,  
141  
Wells, W. F., and Ratcliffe, H. L., The  
behavior of inhaled particles in differ-  
ent states of aerosol suspension as  
indicated by pulmonary tuberculosis  
in rabbits, 412  
Wells, W. F., Measurement of air-borne  
infection by the disinfection of air, 177  
Wheeler, S., and Jones, T., Factors in  
the control of the spread of acute respi-  
ratory infections with reference to  
streptococcal illness and acute rheu-  
matic fever, 58  
White, Paul D., *see* Burrett, John B., 355  
Wilcox, C., *see* Goodwin, R. A., 628  
Wilson, D. Wright, *see* Buchanan, J. M.,  
549  
Winsor, T., *see* Burch, G. E., 226  
Wolff, L., *see* Luisada, A. A., 204  
Wolman, I. J., The intra-duodenal secre-  
tions in childhood, 788  
Woodward, R., *see* Beyer, K. H., 608

